

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/18, 31/19, 31/44, 31/47, 31/195, 31/405, 31/415, 31/425, 31/435, C07C 63/00, 307/06, 307/08, 307/10, C07D 213/89, 217/08, 233/44, 233/88, 239/08, 239/42, 209/40	A1	(11) International Publication Number: WO 95/32710 (43) International Publication Date: 7 December 1995 (07.12.95)
---	----	--

(21) International Application Number: PCT/US95/05938

(22) International Filing Date: 12 May 1995 (12.05.95)

(30) Priority Data:
250,218 27 May 1994 (27.05.94) US

(60) Parent Application or Grant

(63) Related by Continuation
US 250,218 (CIP)
Filed on 27 May 1994 (27.05.94)

(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HARTMAN, George, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). DUGGAN, Mark, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). IHLE, Nathan, C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065

(US). HOFFMAN, William, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

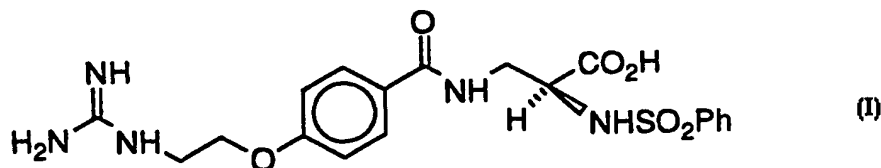
(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published

With international search report.

(54) Title: COMPOUNDS FOR INHIBITING OSTEOCLAST-MEDIATED BONE RESORPTION



(I)

(57) Abstract

Compounds of the following general structure: X-Y-Z-Aryl-A-B, for example (I), which inhibit osteoclast-mediated bone resorption.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

TITLE OF THE INVENTION

COMPOUNDS FOR INHIBITING OSTEOCLAST-MEDIATED BONE RESORPTION

5 BACKGROUND OF THE INVENTION

This invention relates to compounds for inhibiting bone resorption that is mediated by the action of a class of cells known as osteoclasts.

10 Osteoclasts are multinucleated cells of up to 400 μm in diameter that resorb mineralized tissue, chiefly calcium carbonate and calcium phosphate, in vertebrates. They are actively motile cells that migrate along the surface of bone. They can bind to bone, secrete necessary acids and proteases and thereby cause the actual resorption of mineralized tissue from the bone.

15 The pharmacologic activity of these compounds is useful in the treatment of mammals, including man.

The current major bone diseases of public concern are osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular
20 erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid treatment.

All these conditions are characterized by bone loss, resulting from an imbalance between bone resorption (breakdown) and bone formation, which continues throughout life at the rate of about
25 14% per year on the average. However, the rate of bone turnover differs from site to site, for example, it is higher in the trabecular bone of the vertebrae and the alveolar bone in the jaws than in the cortices of the long bones. The potential for bone loss is directly related to turnover and can amount to over 5% per year in vertebrae immediately
30 following menopause, a condition which leads to increased fracture risk.

There are currently 20 million people with detectable fractures of the vertebrae due to osteoporosis in the United States. In addition, there are 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12% mortality

- 2 -

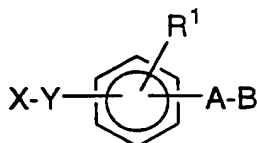
rate within the first two years, while 30% of the patients require nursing home care after the fracture.

Individuals suffering from all the conditions listed above would benefit from treatment with agents which inhibit bone resorption.

5 Endothelial cells secrete growth factors that are mitogenic for endothelium and can induce formation of new blood vessels (angiogenesis). Angiogenic stimuli cause the elongation or proliferation of endothelial cells and generation of new vessels.

10 SUMMARY OF THE INVENTION

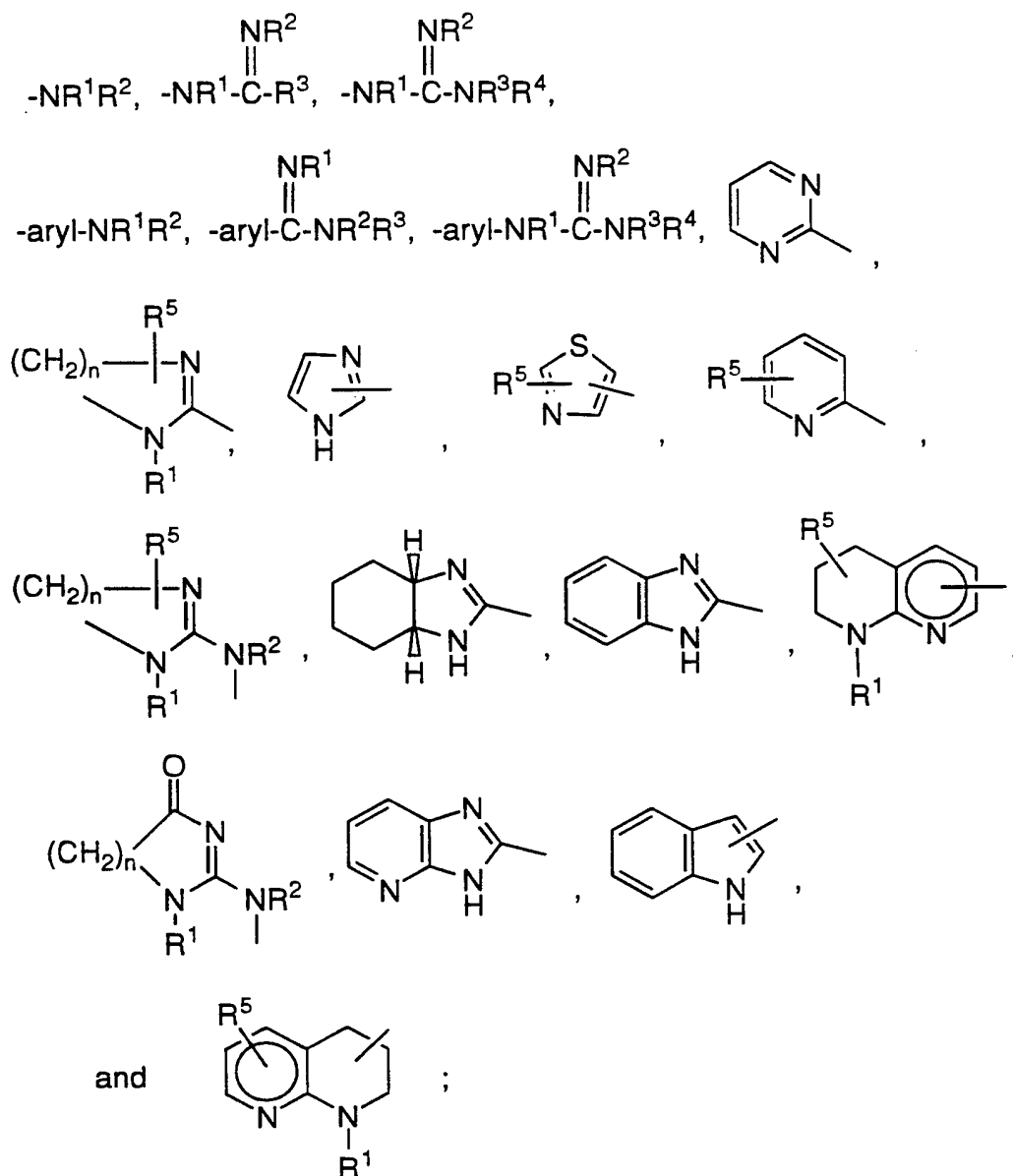
The present invention involves a compound of the formula



wherein

15 X is selected from the group consisting of

- 3 -



Y is selected from the group consisting of

C1-8 alkylene,

$(\text{CH}_2)_m-\text{C}\equiv\text{C}(\text{CH}_2)_n$,

$(\text{CH}_2)_m\text{CR}^1=\text{CR}^2(\text{CH}_2)_n$,

$(\text{CH}_2)_m\text{CR}^1=\text{CR}^2(\text{CH}_2)_n\text{O}$,

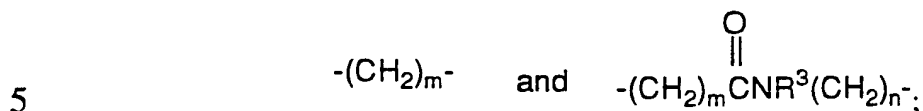
C0-8 alkylene- NR^3 -CO-C0-8 alkylene,

C0-8 alkylene-O-C0-8 alkylene,

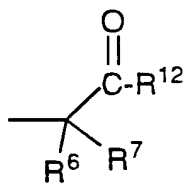
- 4 -

C₀₋₈ alkylene-NR³-C₀₋₈ alkylene and
 C₀₋₈ alkylene-NR³-C₀₋₈ alkylene-O-;

A is selected from the group consisting of



B is



R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- 10 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 15 amino C₀₋₈ alkyl and
 aryl C₀₋₈ alkyl;

.. R⁵ is selected from the group consisting of

- 20 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 amino C₀₋₈ alkyl,
 25 oxo and
 aryl C₀₋₈ alkyl;

- 5 -

R⁶ and R⁷ are each independently selected from the group consisting of:

hydrogen,

C0-6 alkylamino C0-6 alkyl,

C0-6 dialkylamino C0-6 alkyl,

5 aryl C0-6 alkyloxycarbonylamino C0-6 alkyl,

aryl C0-6 alkylsulfonylamino C0-6 alkyl and

aryl C0-6 alkylcarbonylamino C0-6 alkyl;

R¹² is selected from the group consisting of

10 hydroxy,

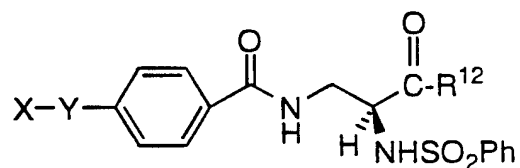
C1-8 alkyloxy,

C1-6 dialkylaminocarbonylmethoxy and

aryl C1-6 dialkylaminocarbonylmethoxy; and

15 m and n are integers independently chosen from 0-6;

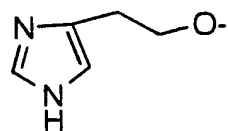
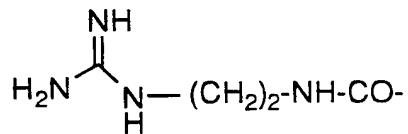
provided that when the compound is



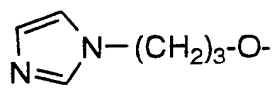
wherein R¹² is hydroxy or C1-4 alkyloxy, then X-Y is not

20 NH₂-(CH₂)₂-NH-CO-,

BOC-HN-(CH₂)₂-NH-CO-,



or

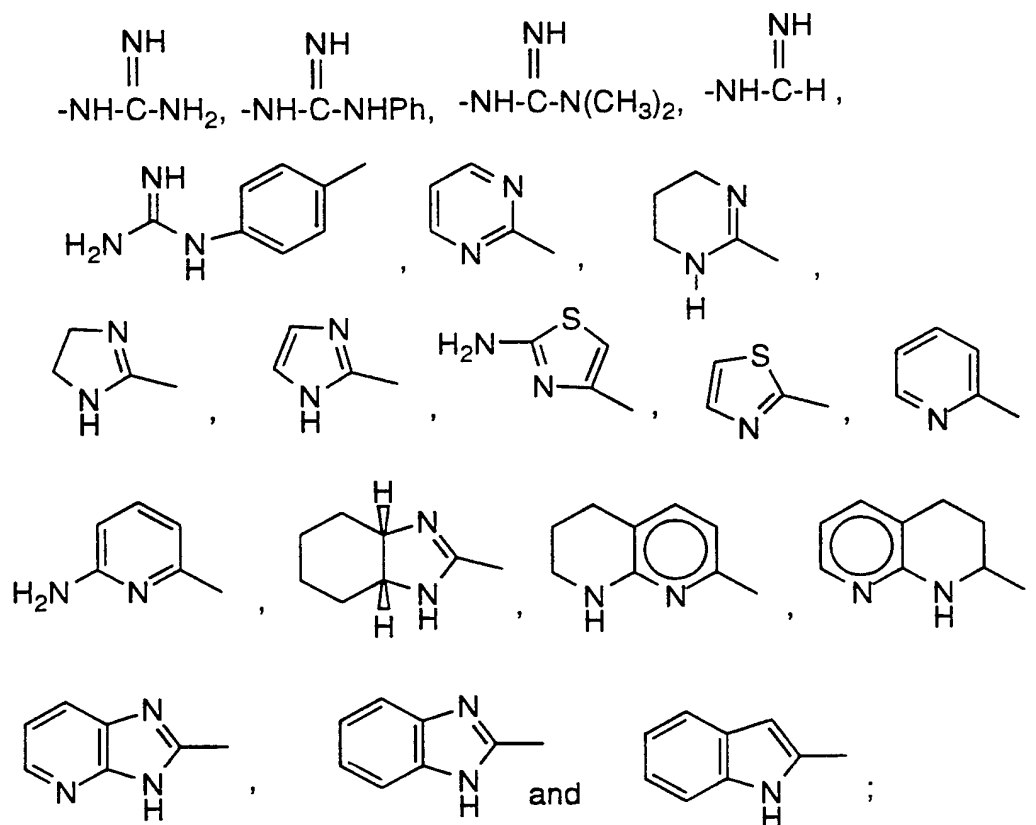


25

- 6 -

and the pharmaceutically acceptable salts thereof.

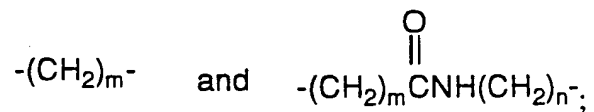
In one embodiment is the compound wherein X is selected from the group consisting of



- 5 Y is selected from the group consisting of
C₁₋₃ alkylene,
-C≡C-,
C₀₋₂ alkylene-NH-CO-,
C₀₋₅ alkylene-O-C₀₋₁ alkylene
10 -NH-C₂₋₄ alkylene and
-NH-C₂₋₄ alkylene-O-;

A is selected from the group consisting of

- 7 -

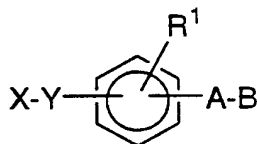


R^1 is selected from the group consisting of
hydrogen and
C₁₋₄ alkoxy;

- 5 R^6 and R^7 are each independently selected from the group consisting of
hydrogen,
-NHCbz,
-NHSO₂Ph,
-NHC(O)-Ph and
10 -N(CH₃)-SO₂Ph; and

m and n are integers independently chosen from 0-6.

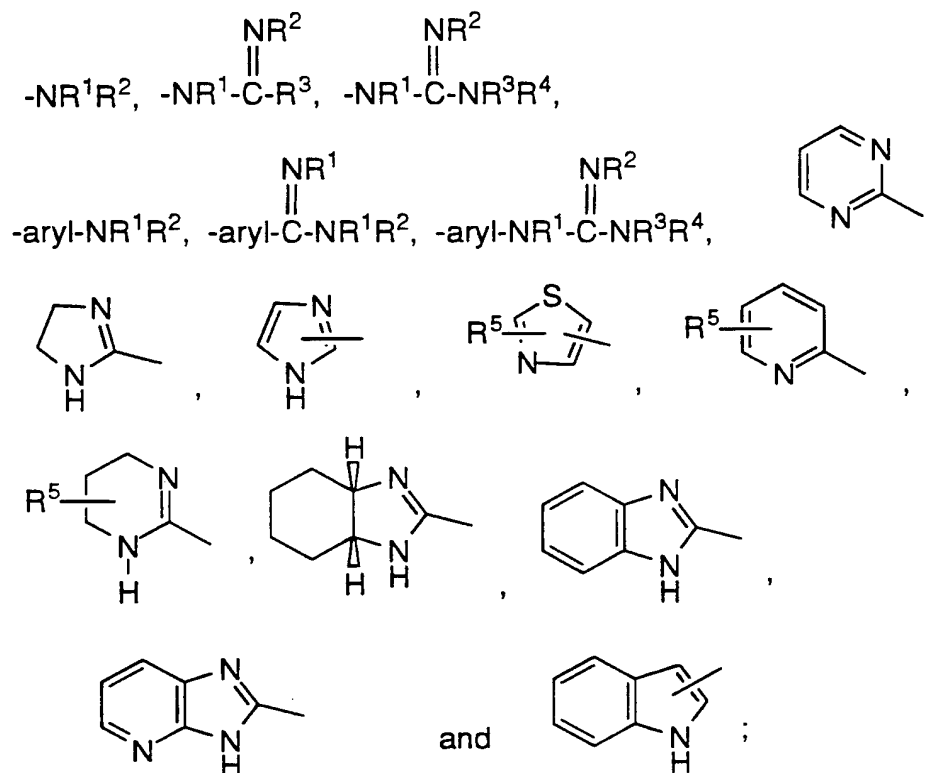
In another embodiment is the compound



15 wherein

X is selected from the group consisting of

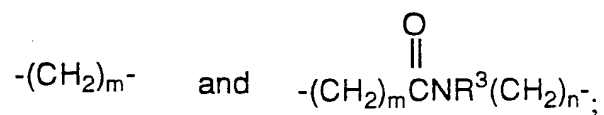
- 8 -



Y is selected from the group consisting of

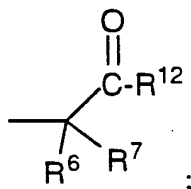
- C₁₋₈ alkylene,
 (CH₂)_m-C≡C(CH₂)_n,
 5 (CH₂)_mCR¹=CR²(CH₂)_n,
 (CH₂)_mCR¹=CR²(CH₂)_nO,
 C₀₋₈ alkylene-NR³-CO-C₀₋₈ alkylene,
 C₀₋₈ alkylene-O-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR³-C₀₋₈ alkylene and
 10 C₀₋₈ alkylene-NR³-C₀₋₈ alkylene-O-;

A is selected from the group consisting of



- 9 -

B is



R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- 5 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 10 amino C₀₋₈ alkyl and
 aryl C₀₋₈ alkyl;

R⁵ is selected from the group consisting of

- hydrogen,
 15 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 amino C₀₋₈ alkyl,
 20 oxo and
 aryl C₀₋₈ alkyl;

R⁶ and R⁷ are each independently selected from the group consisting of:

- hydrogen,
 25 C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylloxycarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl and
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl;

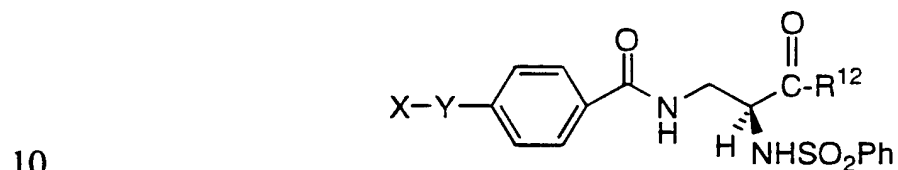
30

- 10 -

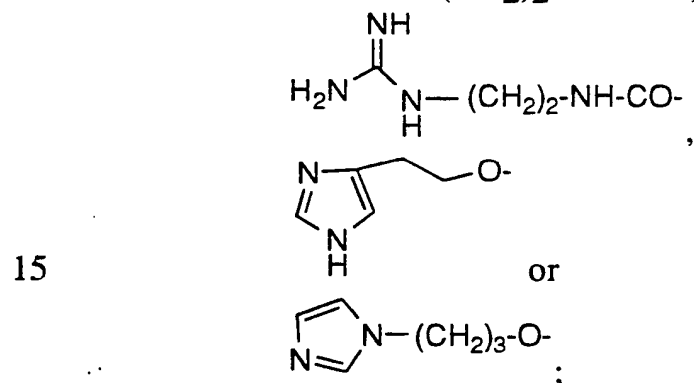
R¹² is selected from the group consisting of
 hydroxy,
 C₁-8 alkyloxy,
 C₁-6 dialkylaminocarbonylmethoxy and
 5 aryl C₁-6 dialkylaminocarbonylmethoxy; and

m and n are integers independently chosen from 0-6;

provided that when the compound is



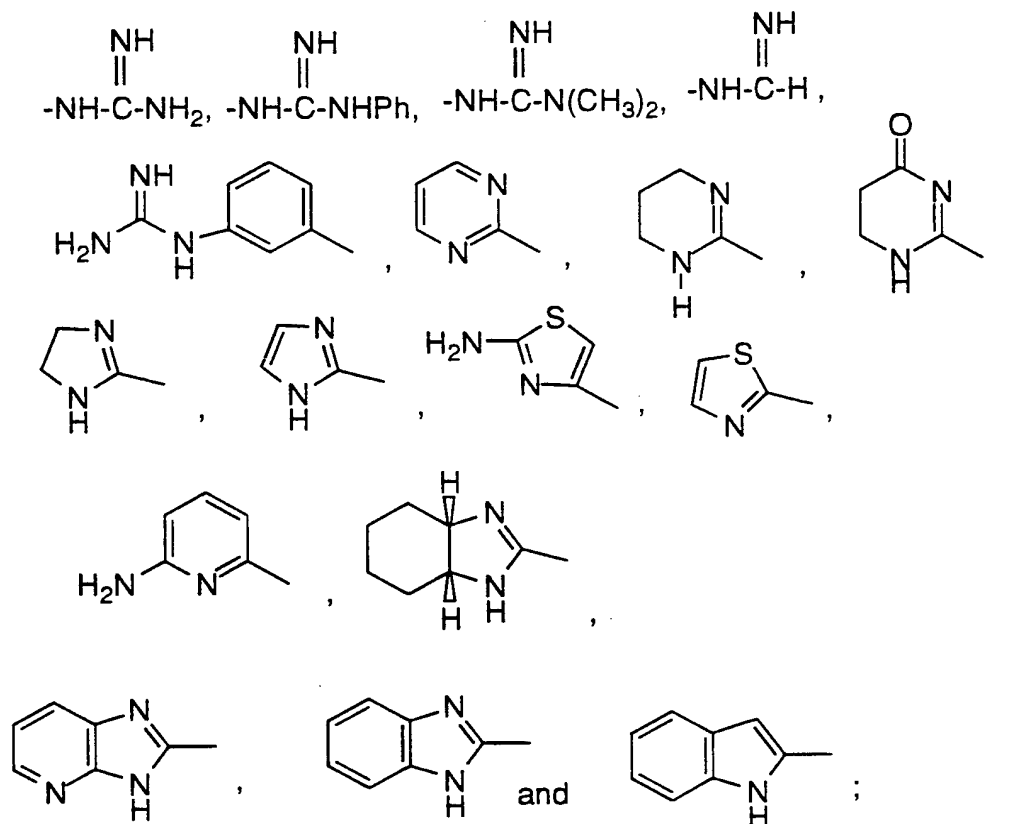
wherein R¹² is hydroxy or C₁-4 alkyloxy, then X-Y is not
 NH₂-(CH₂)₂-NH-CO-,
 BOC-HN-(CH₂)₂-NH-CO-,



and the pharmaceutically acceptable salts thereof.

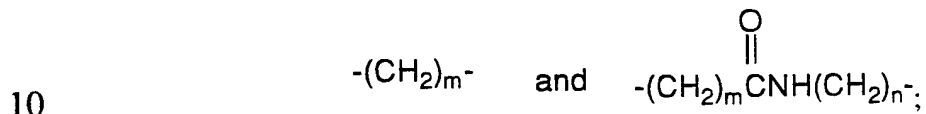
20 In a class of this embodiment is the compound wherein
 X is selected from the group consisting of

- 11 -



- Y is selected from the group consisting of
- C₁₋₂ alkylene,
 - C≡C-,
 - 5 C₀₋₂ alkylene-NH-CO-,
 - C₀₋₅ alkylene-O-C₀₋₁ alkylene and
 - NH-C₂₋₄ alkylene-O-;

A is selected from the group consisting of



R¹ is selected from the group consisting of

- hydrogen and
- C₁₋₄ alkoxy;

- 12 -

R⁶ and R⁷ are each independently selected from the group consisting of
hydrogen,
-NHCbz,
-NHSO₂Ph,
5 -NHC(O)-Ph and
-N(CH₃)-SO₂Ph; and

m and n are integers independently chosen from 0-1.

10 Examples of this class are compounds selected from the
group of:

4-(2-Guanidoethyloxy)phenylcarbonyl-2(S)-benzyloxycarbonylamino-β-
alanine,

15 4-(2-Guanidoethyloxy)phenylcarbonyl-2(S)-phenylsulfonylamino-β-
alanine,

20 2(S)-Phenylsulfonylamino-3-[4-(4-guanidobutyloxy)phenyl]-propionic
acid,

2(S)-(N-Benzyloxycarbonylamino)-3-[4-(5-guanidopentyloxy)phenyl]-
propionic acid,

25 4-(3-Guanidinopropoxy)benzoyl-2-(S)-phenylsulfonylamino-β-
alanine,

4-(3-Formamidinopropoxy)benzoyl-2-(S)-phenylsulfonylamino-β-
alanine,

30 3-Methoxy-4-(3-guanidinopropoxy)benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,

- 13 -

- 3-Methoxy-4-(3-aminopropoxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 5 3-(3-Guanidinopropoxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(N-Phenylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 10 4-[2-(N,N-Dimethylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-(Guanidinophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 15 4-[2-(Guanidino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 3-[2-(Guanidino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 20 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester,
- 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 25 4-[2-(N-(2-Imidazolin-2-yl)aminoethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 30 2(S)-Phenylsulfonylamino-3-[4-(4-(N-imidazolin-2-yl)aminobutyloxy)-phenyl]propionic acid,
- 4-[2-[N-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]amino]-ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,

- 14 -

- 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 5 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester,
- 10 4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2(S)-(N-(2-Imidazolin-2-yl)amino)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 15 4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 20 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino- β -alanine,
- 25 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino- β -alanine,
- Methyl 2(S)-benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)-phenyl]propionate,
- 30 2(S)-Benzoylamino-3-[4-(4-pyrimidin-2-ylamino)butyloxy)phenyl]-propionic acid,
- 2(S)-Benzoylamino-3-[4-(4-(3,4,5,6-tetrahydropyrimidin-2-ylamino)-butyloxy)phenyl]propionic acid,

- 15 -

- 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-sulfonylamino- β -alanine t-butyl ester,
- 5 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-sulfonylamino- β -alanine,
- 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenylsulfonylamino- β -alanine,
- 10 4-[2-(N-(5,6-Dihydro-4-keto-1(H)-pyrimidin-2-yl)amino)ethyloxy]-benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonyl-amino- β -alanine t-butyl ester,
- 15 4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 20 4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine t-butyl ester,
- 25 4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine methyl ester,
- 30 4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine t-butyl ester,

- 16 -

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine,

5 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine,

4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butylester,

10 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,

15 4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine ethyl ester,

20 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β -alanine ethyl ester,

25 4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β -alanine,

4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonylamido- β -alanine ethyl ester,

30 4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonylamido- β -alanine trifluoroacetate,

- 17 -

4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonamido-
β-alanine trifluoroacetate,

4-[3-[N-(1H-Benzimidazo-2-yl)amino]propoxy]benzoyl-2(S)-
5 phenylsulfonylamino-β-alanine t-butyl ester, and

4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-2(S)-
phenylsulfonylamino-β-alanine.

Illustrative of the embodiment is a method of inhibiting the
10 bone resorption activity of mammalian osteoclast cells comprising the
step of administering a pharmacologically effective amount of the
compound.

A further illustration of the embodiment is a composition
for inhibiting bone resorption activity of mammalian osteoclast cells
15 comprising a pharmacologically effective amount of the compound and
a pharmaceutically acceptable carrier.

Exemplifying the class is a method of inhibiting the bone
resorption activity of mammalian osteoclast cells comprising the step of
administering a pharmacologically effective amount of the compound.

20 Further exemplifying the class is a composition for
inhibiting bone resorption activity of mammalian osteoclast cells
comprising a pharmacologically effective amount of the compound and
a pharmaceutically acceptable carrier.

Also included within the scope of the invention is a method
25 of inhibiting the bone resorption activity of mammalian osteoclast cells
comprising the step of administering a pharmacologically effective
amount of a compound of the formula:

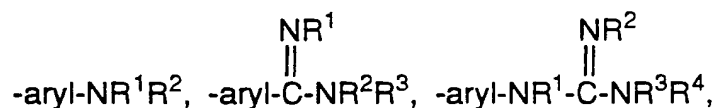
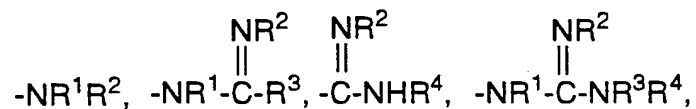


30 wherein:

Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 N atoms
and either unsubstituted or substituted with one or more groups chosen
from R¹ and R²;

- 18 -

X is selected from



- 5 or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R¹³, R¹⁴, R¹⁵ or R¹⁶;

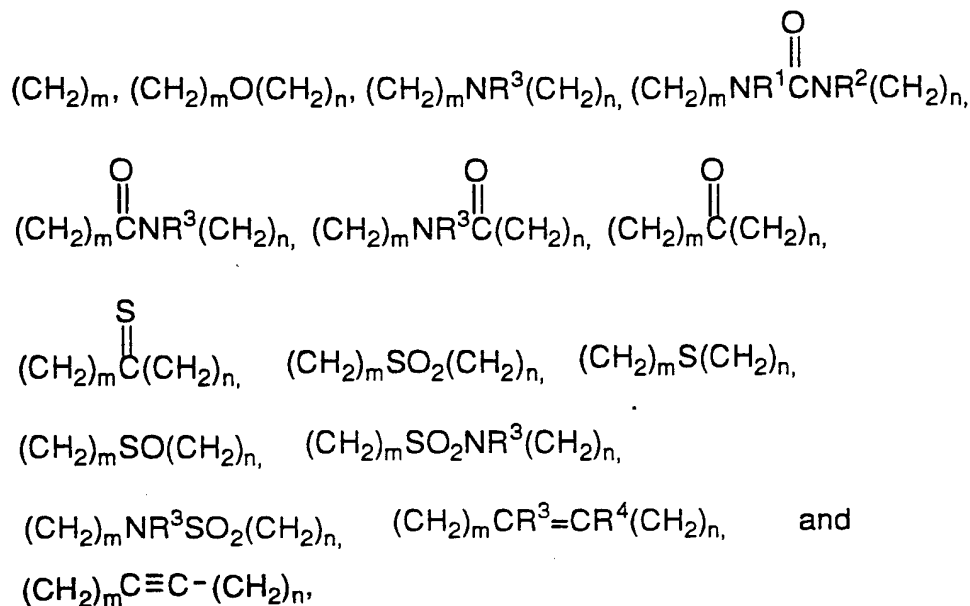
- 10 Y is selected from the group consisting of
 C0-8 alkylene,
 C3-10 cycloalkyl,
 C0-8 alkylene-NR³-CO-C0-8 alkylene,
 C0-8 alkylene-CONR³-C0-8 alkylene,
 C0-8 alkylene-O-C0-8 alkylene,
 15 C0-8 alkylene-NR¹-C0-8 alkylene,
 C0-8 alkylene-S(O)₀₋₂-C0-8 alkylene,
 C0-8 alkylene-SO₂-NR³-C0-8 alkylene,
 C0-8 alkylene-NR³-SO₂-C0-8 alkylene,
 C0-8 alkylene-CO-C0-8 alkylene,
 20 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-NR³-(CH₂)₀₋₆,
 (CH₂)₀₋₆ arylNR³CO(CH₂)₀₋₆

$$\begin{array}{c} \text{OH} \\ | \\ (\text{CH}_2)_{0-8}\text{CH}(\text{CH}_2)_{0-8} \end{array};$$

25

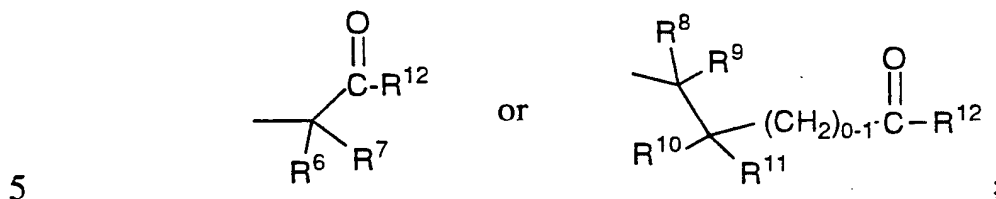
Z and A are each independently selected from the group consisting of

- 19 -



where m and n are integers independently chosen from 0-6;

B is selected from

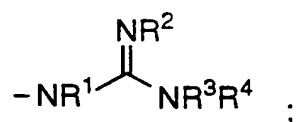
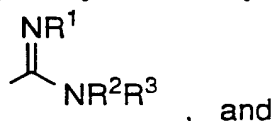


R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- hydrogen,
 halogen,
 10 C₁-10 alkyl,
 aryl C₀-8 alkyl,
 amino C₀-8 alkyl,
 C₁-3 acylamino C₀-8 alkyl,
 C₁-6 alkylamino C₀-8 alkyl,
 15 C₁-6 dialkylamino C₀-8 alkyl,
 aryl C₀-6 alkylamino C₀-6 alkyl,

- 20 -

C1-4 alkoxyamino C0-8 alkyl,
 hydroxy C1-6 alkylamino C0-8 alkyl,
 C1-4 alkoxy C0-6 alkyl,
 carboxy C0-6 alkyl,
 5 C1-4 alkoxycarbonyl C0-6 alkyl,
 carboxy C0-6 alkyloxy,
 hydroxy C1-6 alkylamino C0-6 alkyl,
 hydroxy C0-6 alkyl,



10

R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from

hydrogen,

fluorine,

C1-8 alkyl,

15

hydroxyl,

hydroxy C1-6 alkyl,

carboxy C0-6 alkyl,

C1-6 alkyloxy,

C1-6 alkylcarbonyl,

20

aryl C0-6 alkylcarbonyl,

C1-6 alkylcarbonyloxy,

aryl C0-6 alkylcarbonyloxy,

C1-6 alkylaminocarbonyloxy,

C3-8 cycloalkyl,

25

aryl C0-6 alkyl,

C0-6 alkylamino C0-6 alkyl,

C0-6 dialkylamino C0-6 alkyl,

C1-8 alkylsulfonylamino C0-6 alkyl,

aryl C0-6 alkylsulfonylamino C0-6 alkyl,

- 21 -

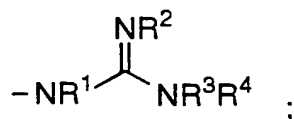
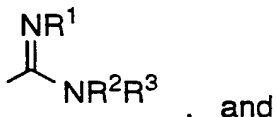
5 C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
10 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
15 aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl, and
aryl C₀₋₆ alkylthiocarbonylamino C₀₋₆ alkyl
20 wherein the alkyl, aryl, or N atoms may be unsubstituted or
substituted with one or more substituents selected from R¹ and
R²;

R¹² is selected from
20 hydroxy,
C₁₋₈ alkyloxy,
aryl C₀₋₆ alkyloxy,
C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
aryl C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
25 C₁₋₆ dialkylaminocarbonylmethyloxy,
aryl C₁₋₆ dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and
wherein the carboxylic acid moiety of said amino acid
is as the free acid or is esterified by C₁₋₆ alkyl; and
30

R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from the group
consisting of
hydrogen,
C₁₋₁₀ alkyl,

- 22 -

- aryl C0-8 alkyl,
 oxo,
 thio,
 amino C0-8 alkyl,
 5 C1-3 acylamino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,
 aryl C0-6 alkylamino C0-6 alkyl,
 C1-4 alkoxyamino C0-8 alkyl,
 10 hydroxy C1-6 alkylamino C0-8 alkyl,
 C1-4 alkoxy C0-6 alkyl,
 carboxy C0-6 alkyl,
 C1-4 alkoxycarbonyl C0-6 alkyl,
 carboxy C0-6 alkyloxy,
 15 hydroxy C1-6 alkylamino C0-6 alkyl,
 hydroxy C0-6 alkyl,



and the pharmaceutically acceptable salts thereof.

- 20 In one embodiment of the method, compounds have the formula:



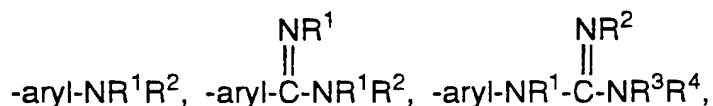
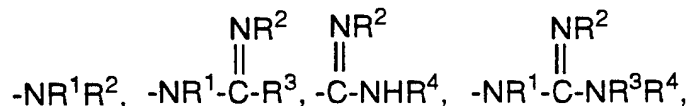
wherein:

25

Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 N atoms and either unsubstituted or substituted with one or more groups chosen from R¹ and R²;

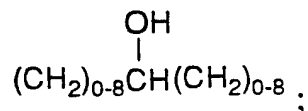
- 23 -

X is selected from



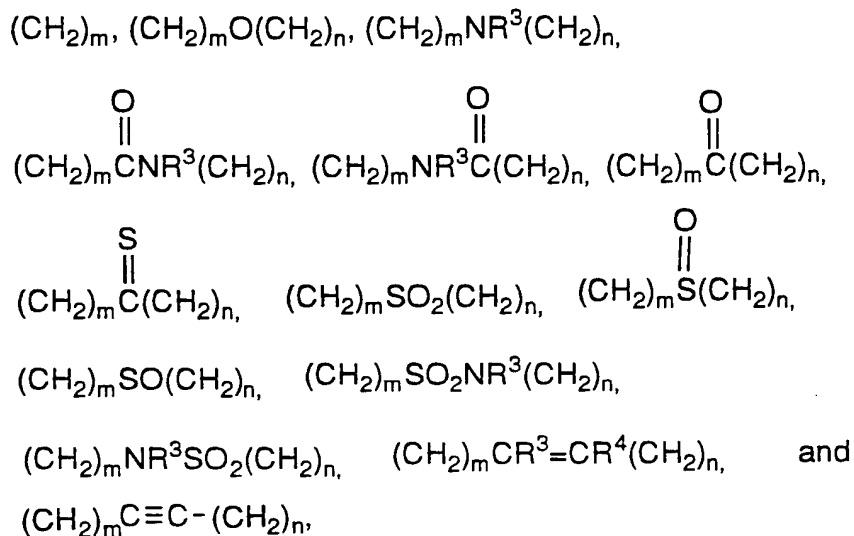
or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R¹³, R¹⁴, R¹⁵ or R¹⁶;

Y is selected from the group consisting of

C₀₋₈ alkylene,C₃₋₁₀ cycloalkyl,C₀₋₈ alkylene-NR³-CO-C₀₋₈ alkylene,C₀₋₈ alkylene-CONR³-C₀₋₈ alkylene,C₀₋₈ alkylene-O-C₀₋₈ alkylene,C₀₋₈ alkylene-NR¹-C₀₋₈ alkylene,C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,C₀₋₈ alkylene-SO₂-NR³-C₀₋₈ alkylene,C₀₋₈ alkylene-NR³-SO₂-C₀₋₈ alkylene,C₀₋₈ alkylene-CO-C₀₋₈ alkylene,(CH₂)₀₋₆ aryl(CH₂)₀₋₆,(CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,(CH₂)₀₋₆ aryl-CO-NH-(CH₂)₀₋₆, and

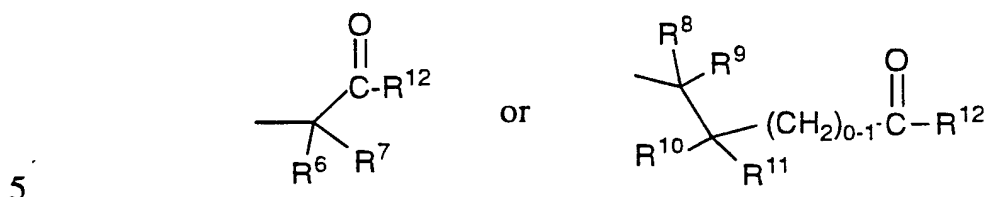
Z and A are each independently selected from the group consisting of

- 24 -



where m and n are integers independently chosen from 0-6;

B is selected from

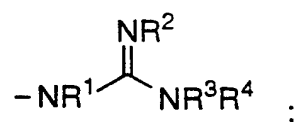
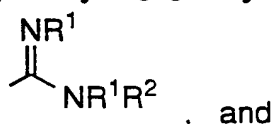


R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- hydrogen,
 halogen,
 10 C₁-10 alkyl,
 aryl C₀-8 alkyl,
 amino C₀-8 alkyl,
 C₁-3 acylamino C₀-8 alkyl,
 C₁-6 alkylamino C₀-8 alkyl,
 15 C₁-6 dialkylamino C₀-8 alkyl,
 aryl C₀-6 alkylamino C₀-6 alkyl,
 C₁-4 alkoxyamino C₀-8 alkyl,

- 25 -

- hydroxy C1-6 alkylamino C0-8 alkyl,
 C1-4 alkoxy C0-6 alkyl,
 carboxy C0-6 alkyl,
 C1-4 alkoxycarbonyl C0-6 alkyl,
 5 carboxy C0-6 alkyloxy,
 hydroxy C1-6 alkylamino C0-6 alkyl,
 hydroxy C0-6 alkyl,



- 10 R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from
 hydrogen,
 fluorine,
 C1-8 alkyl,
 hydroxyl,
 15 hydroxy C1-6 alkyl,
 carboxy C0-6 alkyl,
 C1-6 alkyloxy,
 C1-6 alkylcarbonyl,
 aryl C0-6 alkylcarbonyl,
 20 C1-6 alkylcarbonyloxy,
 aryl C0-6 alkylcarbonyloxy,
 C1-6 alkylaminocarbonyloxy,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 25 C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8 alkyl,

- 26 -

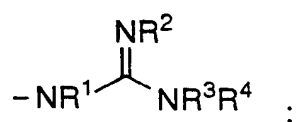
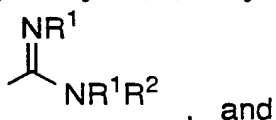
5 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
C1-8 alkylcarbonylamino C0-6 alkyl,
aryl C0-6 alkylcarbonylamino C0-6 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
10 aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
C0-8 alkylaminosulfonylamino C0-6 alkyl,
aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
C1-6 alkylsulfonyl C0-6 alkyl,
aryl C0-6 alkylsulfonyl C0-6 alkyl,
10 C1-6 alkylcarbonyl C0-6 alkyl,
aryl C0-6 alkylcarbonyl C0-6 alkyl,
C1-6 alkylthiocarbonylamino C0-6 alkyl, and
aryl C0-6 alkylthiocarbonylamino C0-6 alkyl
wherein the alkyl or aryl groups may be unsubstituted or
15 substituted with one or more substituents selected from R¹ and
R²;

R¹² is selected from
hydroxy,
20 C1-8 alkyloxy,
aryl C0-6 alkyloxy,
C1-8 alkylcarbonyloxy C1-4 alkyloxy,
aryl C1-8 alkylcarbonyloxy C1-4 alkyloxy,
C1-6 dialkylaminocarbonylmethyloxy,
25 aryl C1-6 dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and
wherein the carboxylic acid moiety of said amino acid
is as the free acid or is esterified by C1-6 alkyl; and

30 R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from the group
consisting of
hydrogen,
C1-10 alkyl,
aryl C0-8 alkyl,

- 27 -

- oxo,
 thio,
 amino C0-8 alkyl,
 C1-3 acylamino C0-8 alkyl,
 5 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,
 aryl C0-6 alkylamino C0-6 alkyl,
 C1-4 alkoxyamino C0-8 alkyl,
 hydroxy C1-6 alkylamino C0-8 alkyl,
 10 C1-4 alkoxy C0-6 alkyl,
 carboxy C0-6 alkyl,
 C1-4 alkoxycarbonyl C0-6 alkyl,
 carboxy C0-6 alkyloxy,
 hydroxy C1-6 alkylamino C0-6 alkyl,
 15 hydroxy C0-6 alkyl,



and the pharmaceutically acceptable salts thereof .

- In a class of this embodiment, the compounds have the
 20 formula wherein Aryl is a 6-membered aromatic ring containing 0, 1 or
 2 N atoms and either unsubstituted or substituted with one or more
 groups chosen from R¹ and R²;

X is defined as above;

- 25 Y is selected from

C0-8 alkylene,
 C0-8 alkylene-NR³-CO-C0-8 alkylene,
 C0-8 alkylene-CONR³-C0-8 alkylene,
 C0-8 alkylene-O-C0-8 alkylene,

- 28 -

C0-8 alkylene-NR¹-C0-8 alkylene,
 C0-8 alkylene-S(O)₀₋₂-C0-8 alkylene,
 C0-8 alkylene-SO₂-NR³-C0-8 alkylene, or
 C0-6 alkylene-aryl-C0-6 alkylene;

5

Z and A are each independently selected from the group consisting of

(CH₂)_m, (CH₂)_mO(CH₂)_n, (CH₂)_m-NR³-(CH₂)_n,

$(\text{CH}_2)_m \overset{\text{O}}{\parallel} \text{CNR}^3 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^3 \overset{\text{O}}{\parallel} \text{C} (\text{CH}_2)_n$,

$(\text{CH}_2)_m \overset{\text{O}}{\parallel} \text{C} (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{SO}_2 (\text{CH}_2)_n$,

$(\text{CH}_2)_m \text{SO}_2 \text{NR}^3 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^3 \text{SO}_2 (\text{CH}_2)_n$,

and $(\text{CH}_2)_m \text{C} \equiv \text{C} - (\text{CH}_2)_n$,

wherein m and n are independently chosen from 0-6;

B is defined as above;

10 R¹, R², R³ and R⁴ are each independently selected from
 hydrogen,

C1-10 alkyl,

aryl C0-8 alkyl,

amino C0-8 alkyl,

15 C1-3 acylamino C0-8 alkyl,

C1-6 alkylamino C0-8 alkyl,

C1-6 dialkylamino C0-8 alkyl,

C1-4 alkyloxy C0-6 alkyl,

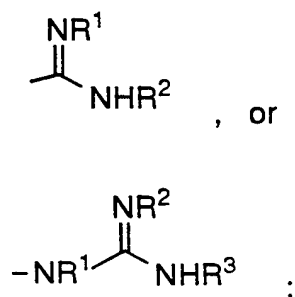
carboxy C0-6 alkyl,

20 C1-4 alkyloxycarbonyl C0-6 alkyl,

carboxy C0-6 alkyloxy,

hydroxy C0-6 alkyl,

- 29 -



R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are independently selected from the group consisting of

- 5 hydrogen,
- hydroxyl,
- fluorine,
- C₁₋₈ alkyl,
- C₃₋₈ cycloalkyl,
- 10 aryl C₀₋₆ alkyl,
- C₀₋₆ alkylamino C₀₋₆ alkyl,
- C₀₋₆ dialkylamino C₀₋₆ alkyl,
- C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
- 15 C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- 20 aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
- aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
- 25 C₁₋₆ alkylcarbonyl C₀₋₆ alkyl, and
- aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl;

R¹² is selected from the group consisting of
hydroxy,

- 30 -

C₁-8 alkyloxy,
 aryl C₀-6 alkyloxy,
 C₁-8 alkylcarbonyloxy C₁-4 alkyloxy, and
 aryl C₁-8 alkylcarbonyloxy C₁-4 alkyloxy; and

5

R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from

hydrogen,

C₁-10 alkyl,

aryl C₀-8 alkyl,

10

oxo,

amino C₀-8 alkyl,

C₁-3 acylamino C₀-8 alkyl,

C₁-6 alkylamino C₀-8 alkyl,

C₁-6 dialkylamino C₀-8 alkyl,

15

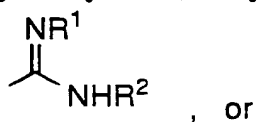
C₁-4 alkyloxy C₀-6 alkyl,

carboxy C₀-6 alkyl,

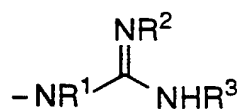
C₁-4 alkyloxycarbonyl C₀-6 alkyl,

carboxy C₀-6 alkyloxy,

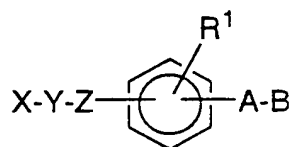
hydroxy C₀-6 alkyl,



20



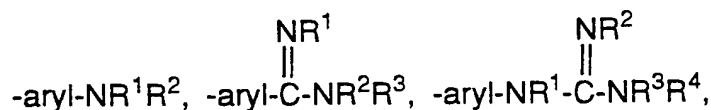
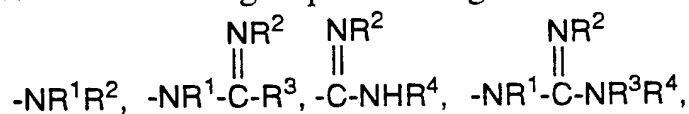
In a subclass of the class is the method wherein the compound has the formula:



25 wherein:

- 31 -

X is selected from the group consisting of

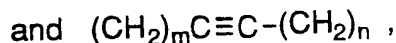
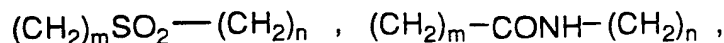
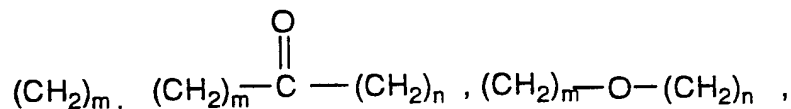


- 5 or a 5- to 10- membered aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N and S and either unsubstituted or substituted with R¹³, R¹⁴, R¹⁵ or R¹⁶;

10 Y is selected from the group consisting of

- C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR³-CO-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CONR³-C₀₋₈ alkylene,
 C₀₋₈ alkylene-O-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR¹-C₀₋₈ alkylene and
 15 C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene;

Z and A are each independently selected from the group consisting of



wherein m and n are independently chosen from 0-6;

20 B is defined as above;

R¹, R², R³ or R⁴, are each independently selected from the group consisting of
 hydrogen,

- 32 -

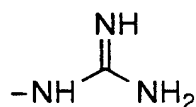
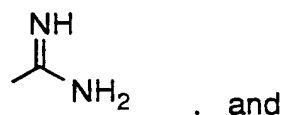
C1-10 alkyl,
 aryl C0-8 alkyl,
 C1-4 alkyloxy C0-6 alkyl,
 C1-4 alkoxycarbonyl C0-6 alkyl,
 5 carboxy C0-6 alkyl,
 hydroxy C0-6 alkyl,
 amino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,
 $\begin{array}{c} \text{NH} \\ \parallel \\ \text{---} \end{array} \text{NH}_2$, and

10 $\begin{array}{c} \text{NH} \\ \parallel \\ \text{---NH} \end{array} \text{NH}_2$; and

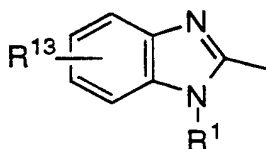
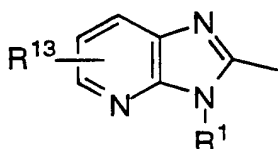
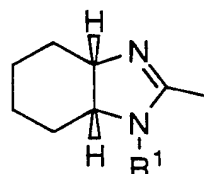
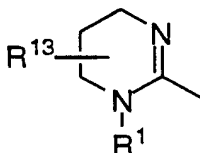
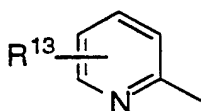
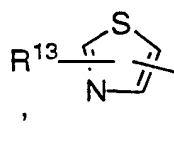
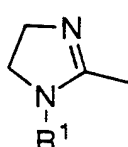
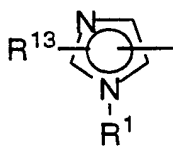
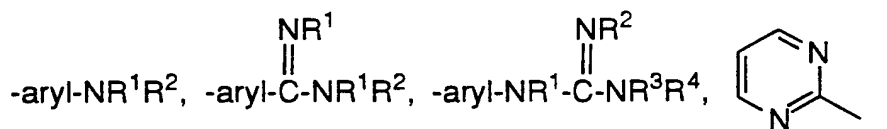
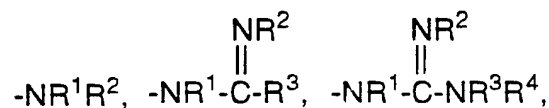
R¹³, R¹⁴, R¹⁵ or R¹⁶, are each independently selected from the group consisting of

15 hydrogen,
 C1-10 alkyl,
 aryl C0-8 alkyl,
 oxo,
 C1-4 alkyloxy C0-6 alkyl,
 C1-4 alkoxycarbonyl C0-6 alkyl,
 20 carboxy C0-6 alkyl,
 hydroxy C0-6 alkyl,
 amino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,

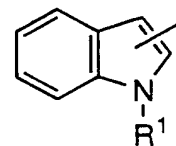
- 33 -



In a group of this subclass is a method wherein X of the compound is selected from the group consisting of



and

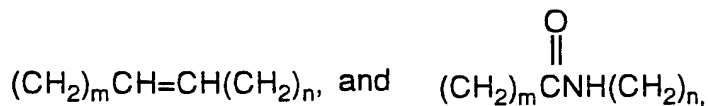
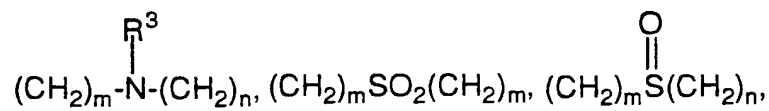
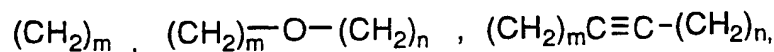


- 5 Y is selected from the group consisting of
 C0-8 alkylene,
 C0-8 alkylene-NR³-CO-C0-8 alkylene,
 C0-8 alkylene-O-C0-8 alkylene and
 C0-8 alkylene-NR¹-C0-8 alkylene;

10

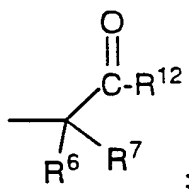
Z and A are each independently selected from the group consisting of

- 34 -



wherein m and n are independently chosen from 0-6;

B is



- 5 $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 are each independently selected from the group consisting of
- hydrogen,
 - C1-4 alkoxy C0-6 alkyl,
 - C1-4 alkoxycarbonyl C0-6 alkyl,
 - 10 C1-6 alkylamino C0-8 alkyl,
 - C1-6 dialkylamino C0-8 alkyl,
 - amino C0-8 alkyl and
 - aryl C0-8 alkyl;
- 15 R^6 and R^7 are each independently selected from the group consisting of:
- hydrogen,
 - C0-6 alkylamino C0-6 alkyl,
 - C0-6 dialkylamino C0-6 alkyl,
 - aryl C0-6 alkyloxycarbonylamino C0-6 alkyl,
 - 20 aryl C0-6 alkylsulfonylamino C0-6 alkyl and
 - aryl C0-6 alkylcarbonylamino C0-6 alkyl;

R^{12} is selected from the group consisting of
hydroxy and

- 35 -

C₁₋₈ alkyloxy; and

R^{13} is selected from the group consisting of

hydrogen,

5

C₁₋₄ alkoxy C₀₋₆ alkyl,

C₁₋₄ alkoxy carbonyl C₀₋₆ alkyl,

C₁-6 alkylamino C₀-8 alkyl,

C₁-6 dialkylamino C₀-8 alkyl,

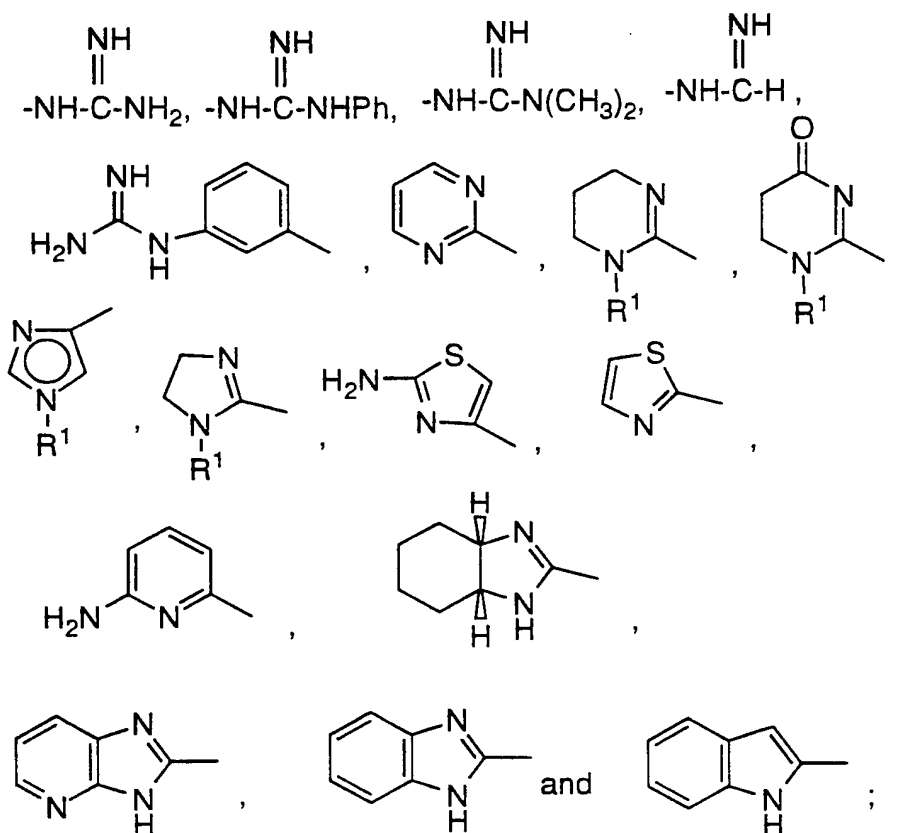
amino C₀₋₈ alkyl,

10

oxo and

aryl C0-8 alkyl.

In a subgroup of this group is a method wherein X of the compound is selected from the group consisting of



15 Y is selected from the group consisting of

- 36 -

C0-2 alkylene,
C0-2 alkylene-NH-CO-,
C0-5 alkylene-O-C0-1 alkylene and
-NH-C2-4 alkylene;

5

R⁶ and R⁷ are each independently selected from the group consisting of
hydrogen,

-NHCbz,

-NHSO₂Ph,

10

-NHC(O)-Ph, and

-N(CH₃)-SO₂Ph.

Exemplifying the subgroup is the method wherein the
compound is selected from the group consisting of:

15

4-(2-Guanidinoethyloxy)benzoyl-2(S)-benzyloxycarbonylamino-β-
alanine,

4-(2-Guanidinoethyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

20

2(S)-Phenylsulfonylamino-3-[4-(4-Guanidinobutyloxy)phenyl]-
propionic acid,

2(S)-(N-Benzyloxycarbonylamino)-3-[4-(5-guanidopentyloxy)phenyl]-
propionic acid,

25

4-(3-Guanidinopropoxy)benzoyl-2(S)-phenylsulfonylamino-β-
alanine,

30

4-(3-Formamidinopropoxy)benzoyl-2(S)-phenylsulfonylamino-β-
alanine,

3-Methoxy-4-(3-Guanidinopropoxy)benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,

- 37 -

- 3-Methoxy-4-(3-aminopropoxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 5 3-(3-Guanidinopropoxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(N-Phenylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 10 4-[2-(N,N-Dimethylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-(Guanidinophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 15 4-[2-(Guanidino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 3-[2-(Guanidino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 20 4-[2-(1-Benzylimidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(Imidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 25 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester,
- 30 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(N-(2-Imidazolin-2-yl)aminoethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,

- 38 -

2(S)-Phenylsulfonylamino-3-[4-(4-(N-imidazolin-2-yl)aminobutyloxy)-phenyl]propionic acid,

5 4-[2-[N-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]amino]-ethyloxybenzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

10 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,

15 4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

20 4-[2(S)-(N-(2-Imidazolin-2-yl)amino)propyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

25 4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine,

30 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine,

Methyl 2(S)-benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)-phenyl]propionate,

- 39 -

2(S)-Benzoylamino-3-[4-(4-pyrimidin-2-ylamino)butyloxy]phenyl]-
propionic acid,

- 5 2(S)-Benzoylamino-3-[4-(4-(3,4,5,6-tetrahydropyrimidin-2-ylamino)-
butyloxy)phenyl]propionic acid,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-
sulfonylamino- β -alanine t-butyl ester,

10

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-
sulfonylamino- β -alanine,

- 15 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-
methyl-N-phenylsulfonylamino- β -alanine,

4-[2-(N-(5,6-Dihydro-4-keto-1(H)-pyrimidin-2-yl)amino)ethyloxy]-
benzoyl-2(S)-phenylsulfonylamino- β -alanine,

- 20 4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonyl-amino- β -
alanine t-butyl ester,

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino- β -
alanine,

25

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -
alanine,

- 30 4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenyl-
sulfonylamino- β -alanine t-butyl ester,

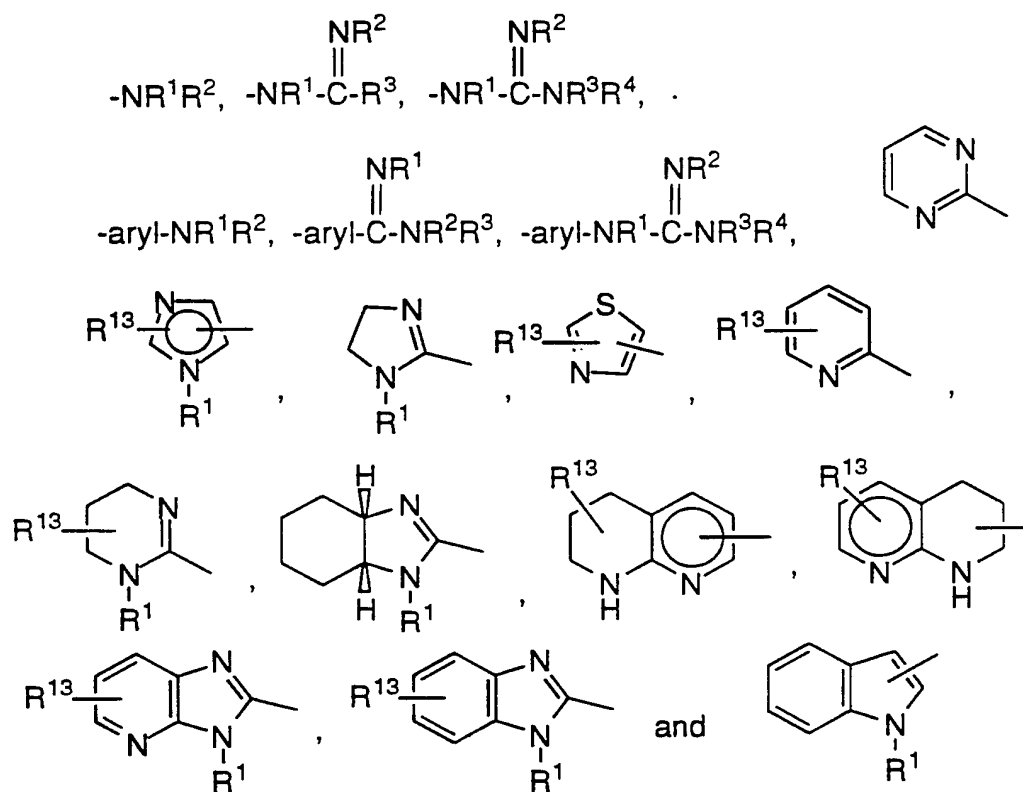
4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-
 β -alanine,

- 40 -

4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine methyl ester, and

4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine.

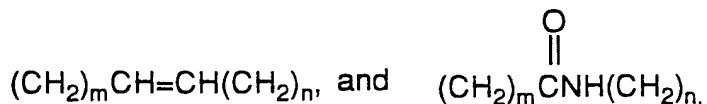
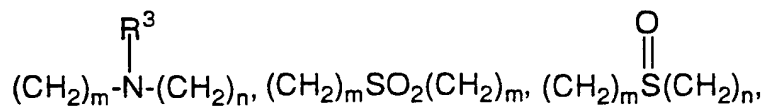
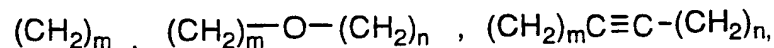
5 In another embodiment of the method of the invention, X of the compound is



Y is selected from the group consisting of
 C0-8 alkylene,
 10 C0-8 alkylene-NR³-CO-C0-8 alkylene,
 C0-8 alkylene-O-C0-8 alkylene and
 C0-8 alkylene-NR¹-C0-8 alkylene;

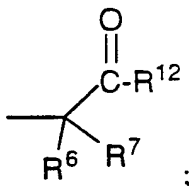
Z and A are each independently selected from the group consisting of

- 41 -



wherein m and n are independently chosen from 0-6;

B is



- 5 $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 are each independently selected from the group consisting of
- hydrogen,
 - C1-4 alkoxy C0-6 alkyl,
 - C1-4 alkoxycarbonyl C0-6 alkyl,
 - 10 C1-6 alkylamino C0-8 alkyl,
 - C1-6 dialkylamino C0-8 alkyl,
 - amino C0-8 alkyl and
 - aryl C0-8 alkyl;
- 15 R^6 and R^7 are each independently selected from the group consisting of:
- hydrogen,
 - C0-6 alkylamino C0-6 alkyl,
 - C0-6 dialkylamino C0-6 alkyl,
 - aryl C0-6 alkyloxycarbonylamino C0-6 alkyl,
 - 20 aryl C0-6 alkylsulfonylamino C0-6 alkyl and
 - aryl C0-6 alkylcarbonylamino C0-6 alkyl;

R^{12} is selected from the group consisting of
hydroxy and

- 43 -

A and B are defined as above;

Y is selected from the group consisting of

- C0-2 alkylene,
- C0-2 alkylene-NH-CO-,
- 5 C0-5 alkylene-O-C0-1 alkylene and
- NH-C2-4 alkylene;

R⁶ and R⁷ are each independently selected from the group consisting of
hydrogen,

- 10 -NHCbz,
- NHSO₂Ph,
- NHC(O)-Ph, and
- N(CH₃)-SO₂Ph.

- 15 Exemplifying the class is a method wherein the compound
is selected from the group consisting of

4-[2-(1H-Imidazo[4,5-6]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-
sulfonylamino-β-alanine t-butyl ester,

20 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-
sulfonylamino-β-alanine,

25 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenyl-
sulfonylamino-β-alanine,

4-[2-(1,8-Naphthydin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonylamino-
β-alanine t-butylester,

30 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-
phenylsulfonylamino-β-alanine t-butyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-
phenylsulfonylamino-β-alanine,

- 44 -

4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonyl-amino- β -alanine ethyl ester,

5 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β -alanine ethyl ester,

10

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamido] β -alanine,

15 4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido- β -alanine ethyl ester,

4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido- β -alanine trifluoroacetate,

20 4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonamido- β -alanine trifluoroacetate,

4-[3-[N-(1H-Benzimidazo-2-yl)amino]propoxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester, and

25

4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-21(S)-phenylsulfonylamino- β -alanine.

DETAILED DESCRIPTION OF THE INVENTION

30

Compounds of the invention are useful for treating mammals suffering from a bone condition caused or mediated by increased bone resorption, who are in need of such therapy. Pharmacologically effective amounts of the compounds, including

- 45 -

pharmaceutically acceptable salts thereof, are administered to the mammal, to inhibit the activity of mammalian osteoclasts.

Compounds of the invention are also useful for inhibiting tumor growth in mammals. Pharmacologically effective amounts of the compounds, including pharmaceutically acceptable salts thereof, are administered to the mammal, to inhibit tumor growth. The growth of tumors depends on an adequate blood supply, which in turn depends on growth of new vessels into the tumor. New vessels are stimulated by factors secreted by the tumor. Inhibition of angiogenesis can cause tumor regression in animals.

Compounds of the invention are also useful for treating and preventing diabetic retinopathy in mammals. Pharmacologically effective amounts of the compounds, including pharmaceutically acceptable salts thereof, are administered to the mammal, to inhibit diabetic retinopathy.

Compounds are also useful in the prevention of restenosis of vessels.

The term "pharmaceutically acceptable salts" means non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts: Acetate, benzene-sulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucoheptanate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, pantothenate, phosphate/diphosphate, polygalactouronate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate. The term also includes acid salts of the compounds, e.g., sodium salts, potassium salts, magnesium salts, etc.

- 46 -

The term "pharmaceutically effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response that is being sought by a researcher or clinician.

The term "aryl" means a mono- or polycyclic system
5 composed of 5- and/or 6- membered aromatic rings containing 0, 1, 2, 3, or 4 heteroatoms chosen from N, O or S and either unsubstituted or substituted. "aryl" with a lower case "a" is defined herein to be broader than the term "Aryl" with a capital "A". One skilled in the art can readily distinguish between the two terms which are clearly defined
10 herein.

The term "bone resorption activity" means the process by which osteoclasts solubilize bone minerals and increase the activity of enzymes that degrade bone matrix.

The term "alkyl" means straight, branched, or cyclic
15 alkane, alkene or alkyne.

The term "alkylene" shall include both straight and branched chain alkylenes (e.g., -CH₂-, -CH(CH₃)-, -CH(CH₃)-CH₂-, etc.).

The term "alkoxy" includes an alkyl portion where alkyl is
20 as defined above.

The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and an aryl portion where aryl is as defined above. The C_{0-n} or C_{1-n} designation where n may be an integer from 1-10 or 2-10 respectively, refers to the alkyl component of
25 the arylalkyl or alkylaryl unit.

The term "halogen" includes fluorine, chlorine, iodine and bromine. The term "oxy" means an oxygen (O) atom. The term "oxo" refers to a bivalent oxygen atom (=O). The term "thio" shall mean a sulfur (S) atom. In the schemes and examples below, various reagent
30 symbols have the following meanings:

The term "L- or D-amino acids" means naturally occurring L- or D-amino acids, for example, those naturally occurring L-amino acids present in humans, e.g. protein amino acids, including L-alanine, L-arginine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamine, L-

- 47 -

glutamic acid, L-glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine, and those naturally occurring D-amino acids which are non-protein amino acids, such as those found, for example, in antibiotic substances produced by bacteria and fungi, including D-valine, D-asparagine, D-glutamate, D-ornithine, D-phenylalanine, D-leucine, D-cysteine, and D-aspartate. (see Zubay "BIOCHEMISTRY" Addison-Wesley Publishing Company, Inc. (Reading, MA) 1983 pp. 867-870 and Stryer "BIOCHEMISTRY" W.H. Freeman and Company (New York, NY) 3rd Edition 1988 pp. 16-21).

	BOC(Boc):	t-butyloxycarbonyl.
	Pd/C:	Palladium on activated carbon catalyst.
	DMF:	Dimethylformamide.
15	DMSO:	Dimethylsulfoxide.
	CBZ(Cbz):	Carbobenzyloxy or benzyloxycarbonyl.
	CH ₂ Cl ₂ :	Methylene chloride.
	CHCl ₃ :	Chloroform.
	EtOH:	Ethanol.
20	NMM:	N-methylmorpholine
	CDI:	Carbonyldiimidazole
	HOBT:	1-Hydroxybenzotriazole
	MeOH:	Methanol.
	EtOAc:	Ethyl acetate.
25	HOAc:	Acetic acid.
	BOP:	Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate.
	DPFN:	3,5-Dimethyl-1-pyrazolylformamidine nitrate
	BH ₃ •DMS	Borane•dimethylsulfide
30	EDC:	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	LDA:	Lithium diisopropylamide
	DME:	1,2-Dimethoxyethane
	DEAD:	Diethyl azodicarboxylate

- 48 -

	Dibal:	Diisobutylaluminum hydride
	THF:	Tetrahydrofuran
	TEA:	Triethylamine
	TFA:	Trifluoroacetic acid
5	DIPEA:	Diisopropylethylamine
	DIAD:	Diisopropyl azodicarboxylate
	PCA•HCl:	Pyrazole carboxamidine hydrochloride

The compounds of the present invention can be
10 administered in such oral dosage forms as tablets, capsules (each of
which includes sustained release or timed release formulations), pills,
powders, granules, elixers, tinctures, suspensions, syrups and emulsions.
Likewise, they may also be administered in intravenous (bolus or
infusion), intraperitoneal, subcutaneous or intramuscular form, all using
15 forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the compounds of the present
invention is selected in accordance with a variety of factors including
type, species, age, weight, sex and medical condition of the patient; the
severity of the condition to be treated; the route of administration, the
20 renal and hepatic function of the patient; and the particular compound
or salt thereof employed. An ordinarily skilled physician or
veterinarian can readily determine and prescribe the effective amount of
the drug required to prevent, counter or arrest the progress of the
condition.

25 Oral dosages of the present invention, when used for the
indicated effects, will range between about 0.01 mg per kg of body
weight per day (mg/kg/day) to about 100 mg/kg/day and preferably 1.0-
100 mg/kg/day and most preferably 1.0 to 20 mg/kg/day.

Intravenously, the most preferred doses will range from about 0.1 to
30 about 10 mg/kg/minute during a constant rate infusion.

Advantageously, compounds of the present invention may be
administered in a single daily dose, or the total daily dosage may be
administered in divided doses of two, three or four times daily.

Furthermore, preferred compounds for the present invention can be

- 49 -

administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar

- 50 -

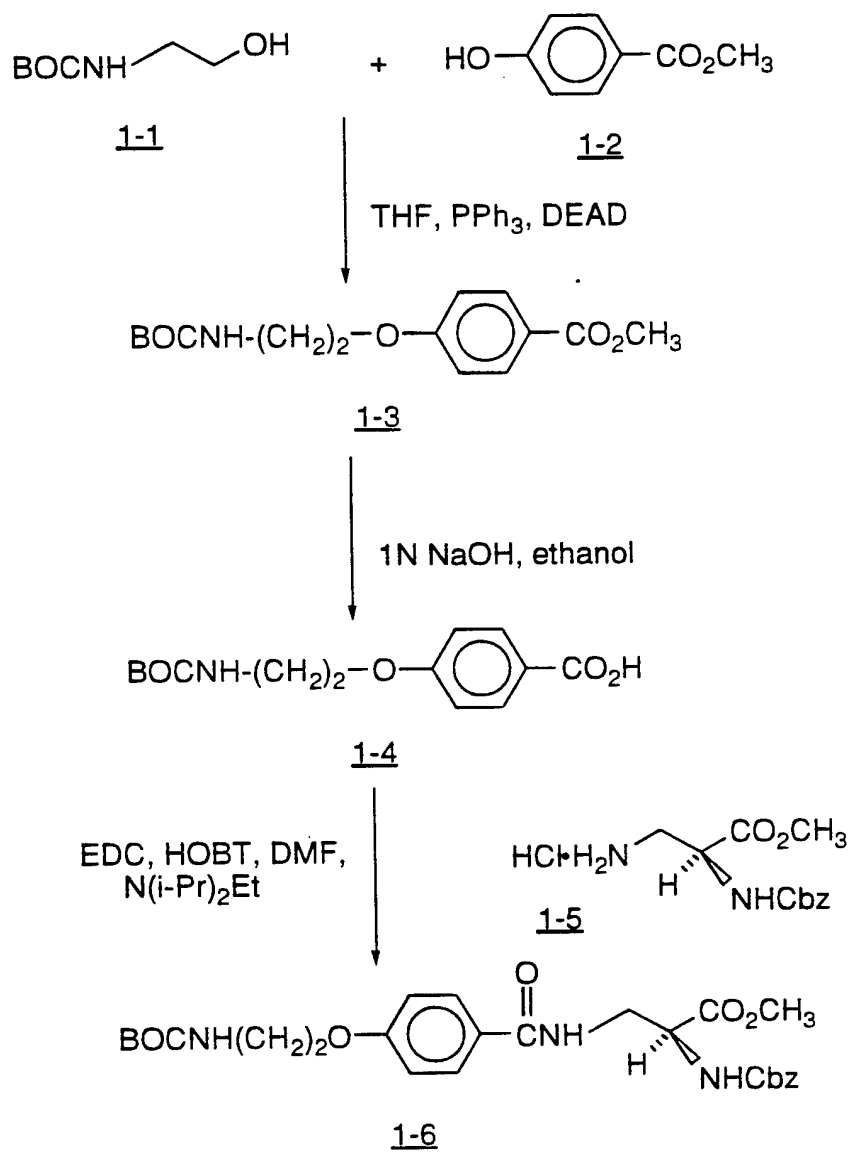
vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

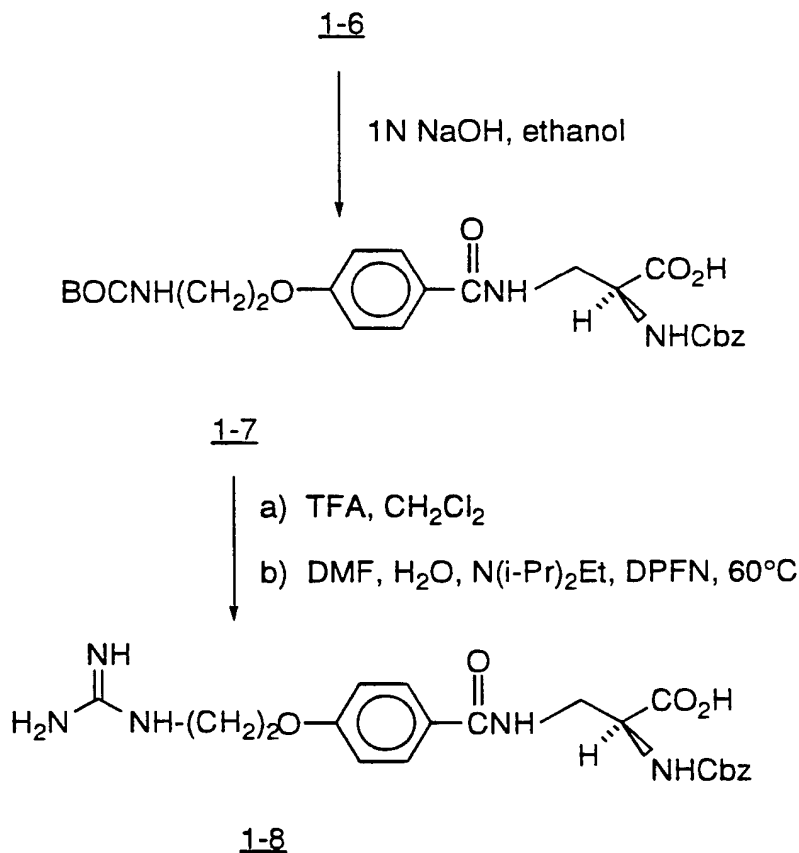
The novel compounds of the present invention were prepared according to the procedure of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

30

- 51 -

SCHEME 1

- 52 -

SCHEME 1 (CONT'D)

5

Methyl 4-(2-N-BOC-Aminoethoxy)benzoate (1-3)

To a stirred solution of 1-2 (1.6 g, 10.5 mmol; Aldrich), PPh₃ (3.4 g, 13.1 mmol), and THF (38 mL) at ambient temperature, was added 1-1 (1.7 g, 10.5 mmol) and DEAD (5.1 mL, 11.0 mmol; 40% toluene solution) in THF (15 mL) dropwise over a 15 min period. After stirring for 20 h the reaction mixture was diluted with EtOAc and then washed with sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 20% EtOAc/hexanes) gave 1-3 as a colorless oil. R_f 0.84 (silica, 30% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, 2H), 6.93 (d, 2H), 5.02 (m, 1H), 4.11 (m, 2H), 3.89 (s, 3H), 3.58 (m, 2H), 1.46 (s, 9H).

- 53 -

4-[2-(N-BOC-Amino)ethyloxy]benzoic acid (1-4)

A mixture of 1-3 (1.3 g, 4.4 mmol), 1N NaOH (26.7 mL, 26.7 mmol) and ethanol (33 mL) was stirred at ambient temperature for 20 h. The reaction mixture was concentrated and the residue dissolved in H₂O (15 mL) and then washed with ether. The aqueous portion was acidified with 10% KHSO₄ and then extracted with EtOAc. The organic phase was washed with brine, dried (MgSO₄) and concentrated to give 1-4 as a white solid. R_f 0.26 (silica, 9:1:1 CH₂Cl₂/CH₃OH/AcOH).

¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, J=9Hz, 2H), 6.96 (d, J=9Hz, 2H), 5.02 (m, 1H), 4.12 (m, 2H), 3.60 (m, 2H), 1.48 (s, 9H).

4-[2-(N-BOC-Amino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine methyl ester (1-6)

To a stirred solution of 1-4 (1.1 g, 4.1 mmol), 1-5 (0.97 g, 4.1 mmol) HOBT (0.55 g, 4.1 mmol), N(i-Pr)₂Et (2.2 mL, 12.3 mmol), and DMF (45 mL) at -15°C was added EDC (0.81 g, 4.1 mmol) followed by removal of the cooling bath. After 72 h the reaction mixture was diluted with EtOAc and then washed with H₂O, sat.

NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 70% EtOAc/hexanes) gave 1-6 as a white powder. R_f 0.64 (silica, EtOAc).

¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J=9Hz, 2H), 7.34 (m, 5H), 6.91 (d, J=9Hz, 2H), 6.80 (m, 1H), 5.95 (m, 1H), 5.13 (m, 2H), 4.99 (m, 1H), 4.55 (m, 1H), 4.08 (m, 2H), 3.85 (m, 2H), 3.80 (s, 3H), 3.56 (m, 2H), 1.47 (s, 9H).

4-[2-(N-BOC-Amino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine (1-7)

Utilizing the procedure for converting 1-3 to 1-4, 1-6 (300 mg, 0.64 mmol) gave 1-7 as a colorless oil. R_f 0.59 (silica, 9:1:1 CH₂Cl₂/CH₃OH/AcOH).

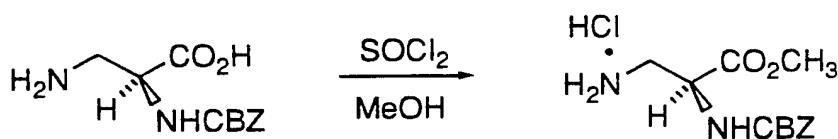
- 54 -

¹H NMR (300 MHz, CDCl₃) δ 7.70 (d, 2H), 7.30 (m, 5H), 6.80 (d, 2H), 6.52 (m, 1H), 5.12 (m, 1H), 5.06 (m, 2H), 4.39 (m, 1H), 4.00-3.50 (m, 6H), 1.46 (s, 9H).

5 4-[2-(Guanido)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino-β-alanine (1-8)

A solution of 1-7 (210 mg, 0.46 mmol), CH₂Cl₂ (3 mL) and TFA (3 mL) was stirred at ambient temperature for 30 min followed by concentration. Most of the excess TFA was then removed azeotropically with toluene. The resulting oil was dissolved in DMF/H₂O (4 mL; 3:1), treated with DIPEA (0.36 mL, 2.5 mmol) and DPFN (0.12 g, 0.65 mmol) and then heated at 60°C for 2 h. The cooled reaction mixture was concentrated and the residual H₂O removed with an ethanol azeotrope. Flash chromatography (silica, 10:0.8:0.8 ethanol/NH₄OH/H₂O) gave 1-8 as a white powder. R_f 0.25 (silica, 10:1:1 ethanol/NH₄OH/H₂O).

¹H NMR (400 MHz, CD₃OD) δ 7.53 (d, J=9Hz, 2H), 7.06 (m, 5H), 6.74 (d, J=9Hz, 2H), 4.81 (m, 2H), 4.03 (m, 1H), 3.94 (t, J=5Hz, 2H), 3.48 (m, 2H), 3.36 (t, J=5Hz, 2H).



1-5

Methyl 3-amino-2(S)-benzyloxycarbonylamino propionate hydrochloride (1-5)

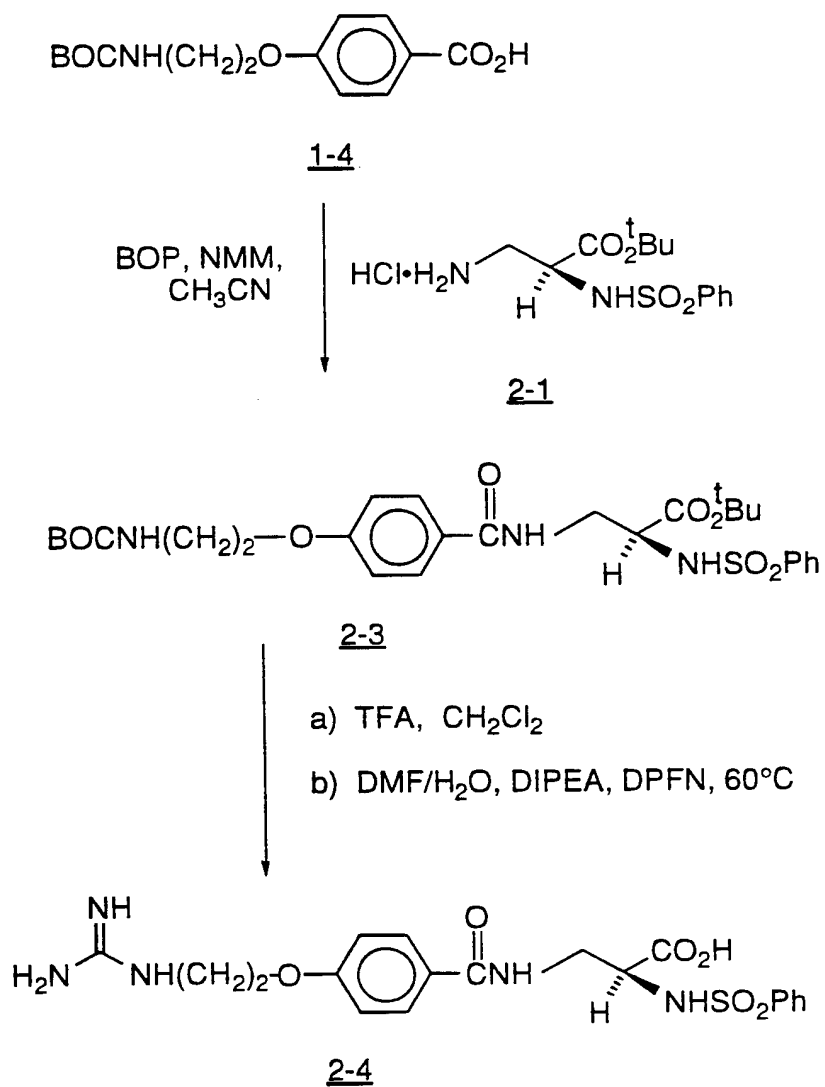
3-Amino-2(S)-benzyloxycarbonylamino propionic acid (Fluka) (5.0 g, 21.0 mmoles) was suspended in MeOH and at -10° SOCl₂ (23.0 mmoles) was added. The reaction mixture was allowed to gradually warm to room temperature over 16 h. The solvent was then removed and the resulting solid was triturated with Et₂O to give 1-5.

- 55 -

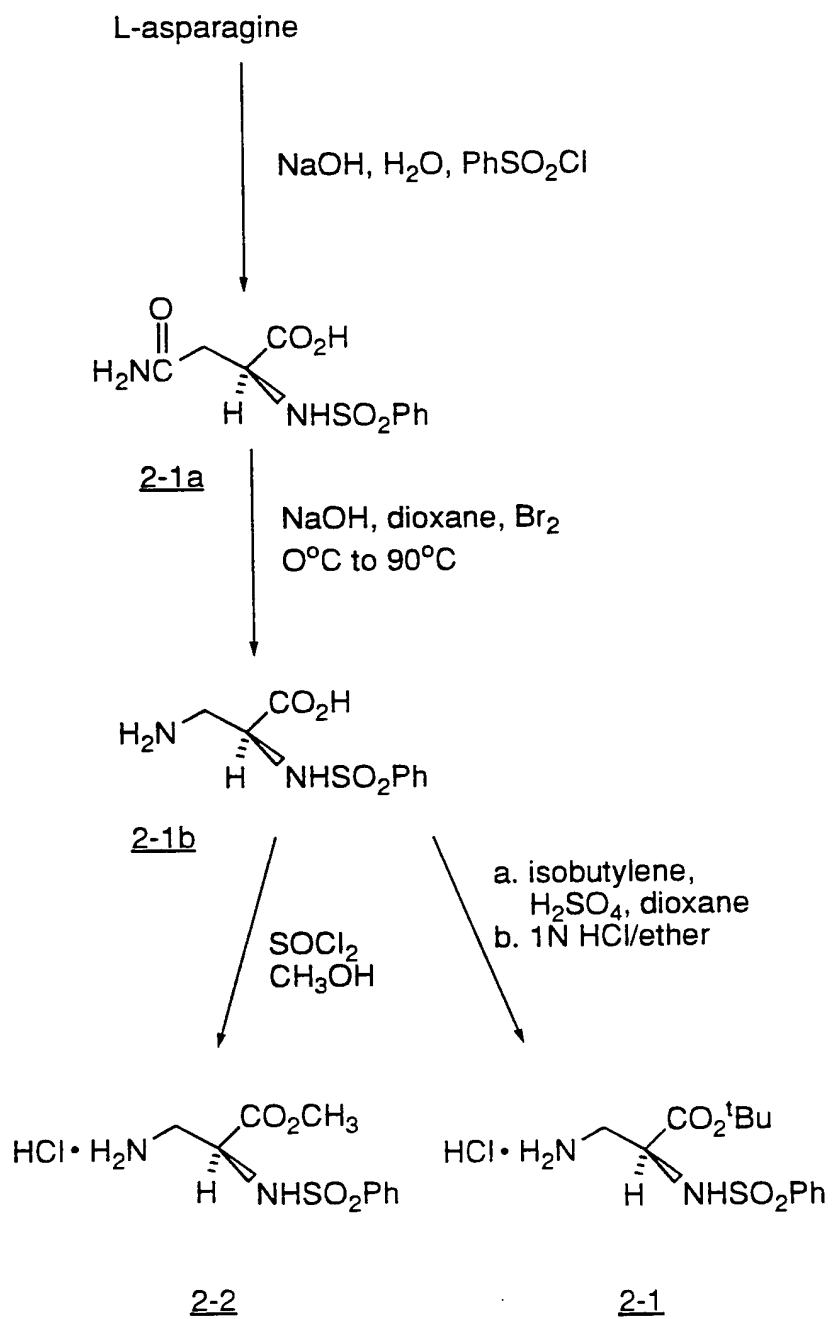
^1H NMR (300 MHz, D_2O) δ 3.32 (2H, m), 3.52 (2H, m), 3.70 (1H, m), 3.80 (4H, m), 4.59 (1H, m), 5.18 (3H, s), 7.45 (5H, s).

SCHEME 2

5



- 56 -

SCHEME 2 (CONT'D)

- 57 -

tert-Butyl 3-amino-2(S)-phenylsulfonylaminopropionate hydrochloride
(2-1)

In a Fischer-Porter tube, a mixture of 2-1b (10.2 g, 42 mmol) and DME (150 mL) was sequentially treated with H₂SO₄ (6.4 mL, 0.12 mol), cooled to -78°C, and then condensed isobutylene (75 mL). The cooling bath was removed. After 24 h, ice/water (250 mL) was added followed by washing with ether (2x). The aqueous phase was basified with aq 6N NaOH, then saturated with NaCl, followed by extraction with EtOAc (3x). The combined extracts were washed with brine, dried (MgSO₄), and concentrated to give a white solid. This was dissolved in CH₂Cl₂ and treated with 1N HCl/ether (22 mL), and then concentrated to give 2-1 as a glassy yellow solid.
¹H NMR (400 MHz, DMSO) δ 8.25-8.00 (m, 4H), 7.85-7.58 (m, 5H), 4.08 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 1.17 (s, 9H).

4-[2-(N-BOC-Amino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine tert-butyl ester (2-3)

To a stirred solution of 1-4 (200 mg, 0.71 mmol), 2-1 (260 mg, 0.85 mmol), NMM (313 μL, 2.8 mmol), and CH₃CN (4 mL) at ambient temperature was added BOP reagent (473 mg, 1.1 mmol). After 20 h the reaction mixture was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 40% EtOAc/hexanes) gave 2-3 as a white solid. R_f 0.19 (silica, 40% EtOAc/hexanes).
¹H NMR (300 MHz, CD₃OD) δ 7.77 (m, 2H), 7.67 (d, J=9Hz, 2H), 7.42 (m, 3H), 6.92 (d, J=9Hz, 2H), 4.02 (m, 3H), 3.59 (dd, 1H), 3.42 (dd, 1H), 3.38 (m, 2H), 1.38 (s, 9H), 1.16 (s, 9H).

4-[2-(Guanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (2-4)

A solution of 2-3 (340 mg, 0.64 mmol), TFA (3 mL), and CH₂Cl₂ (3 mL) was stirred at ambient temperature for 1.0 h. Concentration, followed by azeotropic removal of the residual TFA,

- 58 -

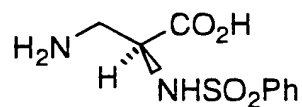
with toluene, gave an oil which was dissolved in DMF/H₂O (3 mL; 3:1) and then treated with N(i-Pr)₂Et (334 μ L, 1.9 mmol) and DPFN (193 mg, 0.95 mmol). This solution was heated at 60°C for 4 h and the cooled reaction mixture concentrated. Flash chromatography (silica, 10/0.2/0.2 to 10/1/1 ethanol/NH₄OH/H₂O) gave 2-4 as a white powder. R_f 0.20 (silica, 10/1/1 ethanol/NH₄OH/H₂O).

¹H NMR (400 MHz, D₂O) δ 7.62 (m, 2H), 7.43 (d, J=9Hz, 2H), 7.18 (m, 3H), 6.93 (d, J=9Hz, 2H), 4.18 (m, 2H), 3.72 (m, 1H), 3.55 (m, 3H), 3.19 (m, 1H).

N-Phenylsulfonyl-L-asparagine (2-1a)

To a stirred solution of L-asparagine (Aldrich) (10 g, 76 mmol), NaOH (3.4 g, 85 mmol), H₂O (50 mL), and dioxane (50 mL) at 0°C was added PhSO₂Cl (10.6 mL, 84 mmol). After 1 min, NaOH (3.4 g) in H₂O (50 mL) was added and the reaction mixture stirred for 30 MIN. The reaction mixture was then concentrated to remove dioxane then washed with EtOAc. The aqueous phase was then cooled to 0°C and acidified to pH 5.0 with conc. HCl to effect product precipitation. The resulting solid was collected by filtration, washed with H₂O (20 mL) and dried at 50°C under vacuum to give N-phenylsulfonyl-L-asparagine (2-1a) as a white solid.

R_f 0.40 (silica, 10:1:1 ethanol/H₂O/NH₄OH). ¹H NMR (300 MHz, D₂O) δ 7.59 (m, 2H), 7.26 (m, 3H), 3.92 (m, 1H), 3.02 (m, 1H), 2.35 (m, 1H).



3-Amino-2(S)-phenylsulfonylaminopropionic acid (2-1b)

To stirred solution of NaOH (15.6 g, 0.4 mol) in H₂O (70 mL), cooled with an icebath, was added bromine (3.6 mL, 0.07 mol) dropwise. After 5 min, a cold solution of N-phenylsulfonyl-L-asparagine 2-1a (14.6 g, 54 mmol) and NaOH (4.3 g, 0.1 mol) in H₂O (50 mL) was added in one portion. The solution was stirred for 20 min

- 59 -

at 0°C then 30 min at 90°C. The reaction mixture was recooled to 0°C, and the pH adjusted to 7 through dropwise addition of conc. HCl. The white precipitate formed was collected by filtration and then dried to give (2-1b) as a white solid. ¹H NMR (300 MHz, D₂O) δ 8.00-7.50 (m, 5H), 3.88 (m, 1H), 3.37 (m, 1H), 3.12 (m, 1H).

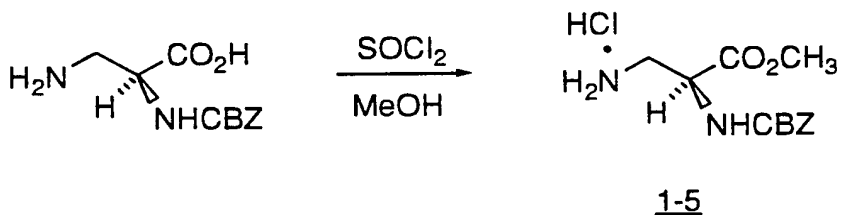
Methyl 3-Amino-2(S)-phenylsulfonylaminopropionate hydrochloride
(2-2)

To a stirred solution of 2-1b (5.0 g, 21 mmol) in CH₃OH (100 mL) at 0°C was added SOCl₂ (7.5 mL, 100 mmol) dropwise. The cooling bath was then removed and the solution stirred at ambient temperature for 20 h. Concentration and trituration with ether gave 2-2 as a white solid. ¹H NMR (300 MHz, D₂O) δ 7.82-7.50 (m, 5H), 4.32 (m, 1H), 3.40 (m, 1H), 3.32 (s, 3H), 3.10 (m, 1H).

tert-Butyl 3-amino-2(S)-phenylsulfonylaminopropionate hydrochloride
(2-1)

In a Fischer-Porter tube, a mixture of 2-1b (10.2 g, 42 mmol) and DME (150 mL) was sequentially treated with H₂SO₄ (6.4 mL, 0.12 mol), cooled to -78°C, and then condensed isobutylene (75 mL). The tube was sealed and the cooling bath was removed. After 24 h, ice/water (250 mL) was added followed by washing with ether (2x). The aqueous phase was basified with aq 6N NaOH, then saturated with NaCl, followed by extraction with EtOAc (3x). The combined extracts were washed with brine, dried (MgSO₄), and concentrated to give a white solid. This was dissolved in CH₂Cl₂ and treated with 1N HCl/ether (22 mL), and then concentrated to give 2-1 as a glassy yellow solid. ¹H NMR (400 MHz, DMSO) δ 8.25-8.00 (m, 4H), 7.85-7.58 (m, 5H), 4.08 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 1.17 (s, 9H).

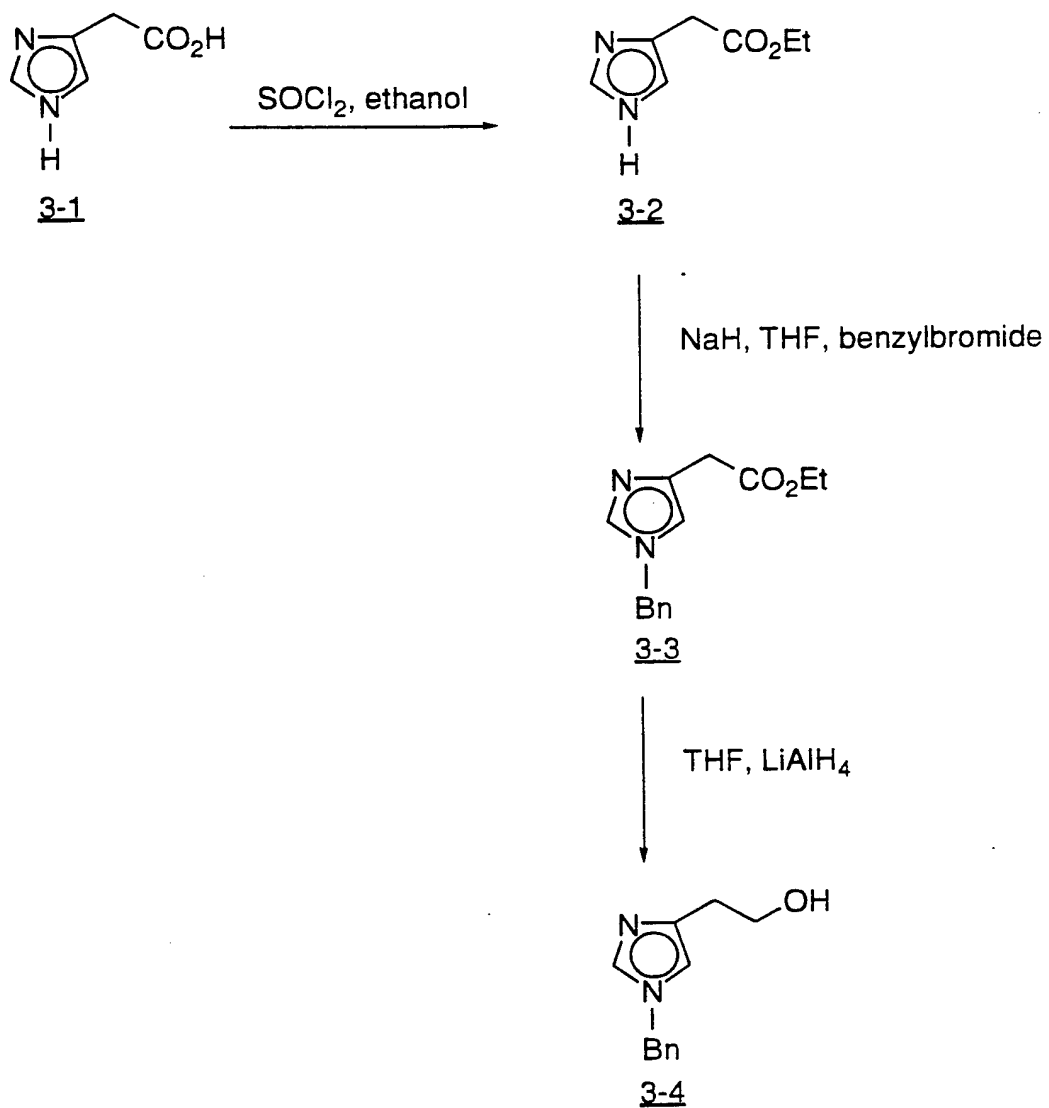
- 60 -



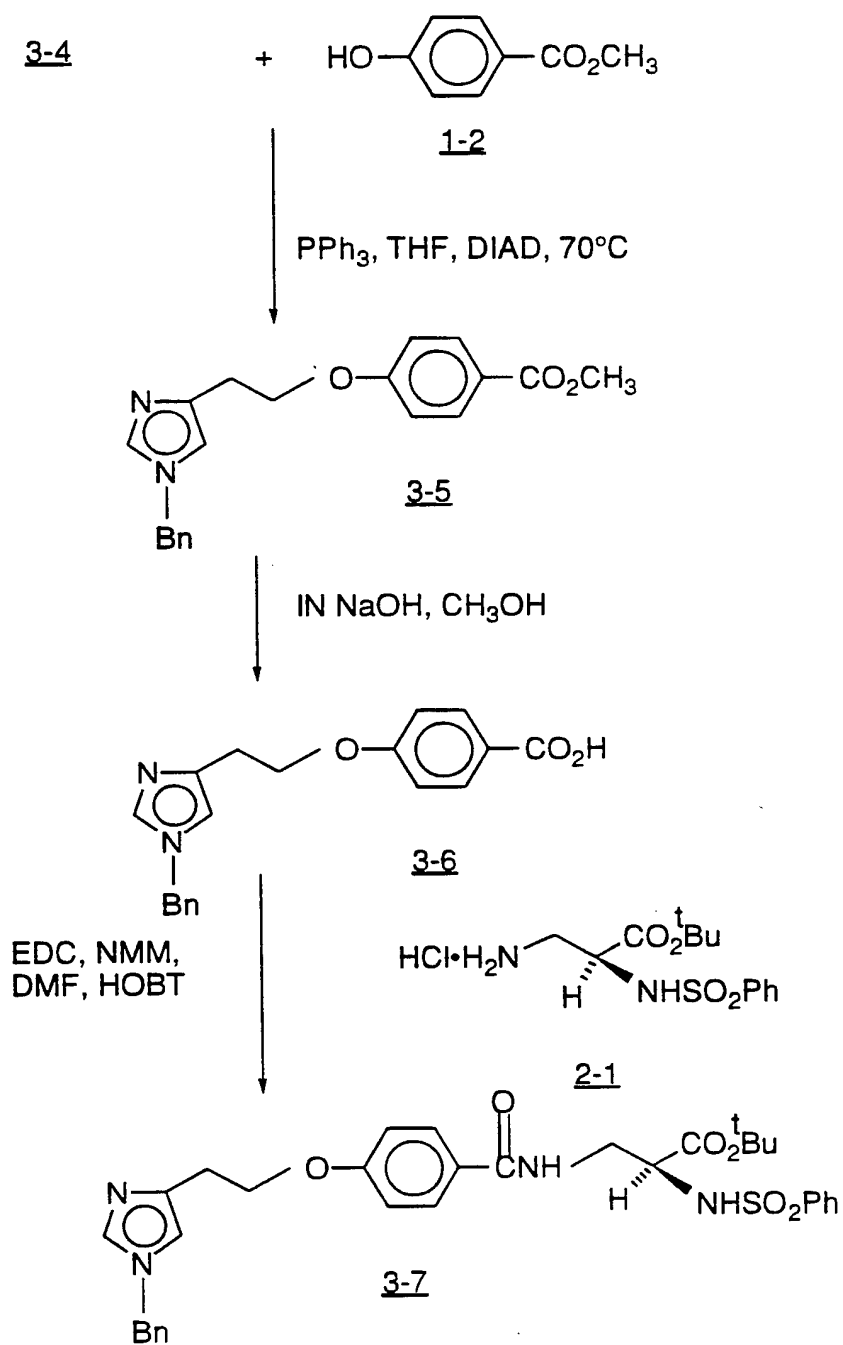
Methyl 3-amino-2(S)-benzyloxycarbonylaminopropionate hydrochloride (1-5)

- 5 3-Amino-2(S)-benzyloxycarbonylaminopropionic acid (Fluka) (5.0 g, 21.0 mmol) was suspended in MeOH and at -10°C SOCl₂ (1.7 mL, 23.0 mmol) was added. The reaction mixture was allowed to gradually warm to room temperature over 16 h. The solvent was then removed and the resulting solid was triturated with Et₂O to give
- 10 1-5.
¹H NMR (300 MHz, D₂O) δ 7.45 (s, 5H), 5.18 (s, 3H), 4.59 (m, 1H), 3.80 (m, 4H), 3.70 (m, 1H), 3.52 (m, 2H), 3.32 (m, 2H).

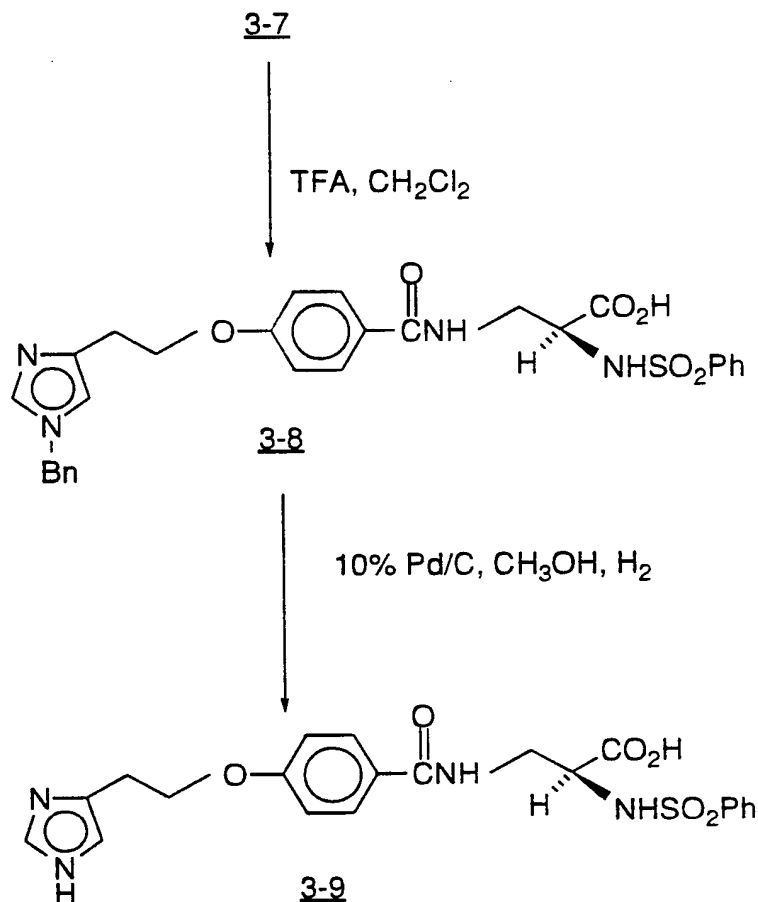
- 61 -

SCHEME 3

- 62 -

SCHEME 3 (CONT'D)

- 63 -

SCHEME 3 (CONT'D)5 Ethyl imidazol-4-ylacetate (3-2)

To a suspension of 3-1 (5.0 g, 30.7 mmol, Aldrich) in ethanol (100 mL) at ambient temperature was added SOCl₂ (11.2 mL, 154 mmol) dropwise. After stirring overnight the homogenous solution was concentrated and the residue suspended in CH₂Cl₂ and washed with

10 sat. NaHCO₃. The sat. NaHCO₃ was back-extracted with CH₂Cl₂. The CH₂Cl₂ portions were combined, dried (MgSO₄), and concentrated to give 3-2 as a pale yellow liquid.

¹H NMR (300 MHz, CDCl₃) δ 7.60 (s, 1H), 6.97 (s, 1H), 4.10 (q, 2H), 3.67 (s, 2H), 1.24 (t, 3H).

- 64 -

Ethyl 1-Benzylimidazol-4-ylacetate (3-3)

A THF (15 mL) solution of 3-2 (3.8 g, 24.6 mmol), was added dropwise to a stirred suspension of NaH (1.1 g, 26.5 mmol) in THF (25 mL) at 0°C over 30 min. The cooling bath was then removed and the mixture stirred at ambient temperature for 3 h followed by dropwise addition of benzyl bromide (24.6 mmol) over 30 min. After 20 h the solvent was evaporated and the residue partitioned between CH₂Cl₂ and H₂O. The organic phase was washed with H₂O, dried (MgSO₄), and concentrated. Flash chromatography (silica, 40% (CHCl₃/NH₃)/EtOAc) gave 3-3 as a pale yellow oil. R_f 0.15 (silica, 40% (CHCl₃/NH₃)/EtOAc)).

¹H NMR (300 MHz, CDCl₃) δ 7.52 (s, 1H), 7.40-7.10 (m, 5H), 6.87 (s, 1H), 5.08 (s, 2H), 4.15 (q, 2H), 3.62 (s, 2H), 1.26 (t, 3H).

2-(1-Benzylimidazol-4-yl)ethanol (3-4)

To a stirred solution of 3-3 (4.6 g, 19 mmol) in THF (50 mL) at ambient temperature was added LiAlH₄ (9.4 mL, 9.4 mmol; 1M THF solution). After 1.0 h the reaction was quenched with sat. NaK tartrate solution. The mixture was poured into a EtOAc/H₂O mixture. The organic portion was washed with brine, dried (MgSO₄) and concentrated to give 3-4 as a yellow viscous oil.

¹H NMR (300 MHz, CDCl₃) δ 7.44 (s, 1H), 7.40-7.10 (m, 5H), 6.68 (s, 1H), 5.03 (s, 2H), 3.87 (t, J=6 Hz, 2H), 2.77 (t, J=6 Hz, 2H).

Methyl 4-[2-(1-Benzylimidazol-4-yl)ethoxy]benzoate (3-5)

A solution of 1-2 (152 mg, 1.0 mmol), PPh₃ (341 mg, 1.3 mmol), and THF (20 mL) was treated dropwise with DIAD (256 µL, 1.3 mmol) and 3-4 (202 mg, 1.0 mmol) in THF (10 mL) over a 30 min period and then heated at 70° overnight. After 72 h, the reaction mixture was concentrated and then subjected to flash chromatography (silica, 40% (CHCl₃/NH₃)/EtOAc) to give 3-5 as a colorless oil. R_f 0.16 (silica, 40% (CHCl₃/NH₃)/EtOAc).

¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, J=9Hz, 2H), 7.46 (s, 1H), 7.40-

- 65 -

7.10 (m, 5H), 6.89 (d, J=9Hz, 2H), 6.74 (s, 1H), 5.04 (s, 2H), 4.28 (t, J=6Hz, 2H), 3.85 (s, 3H), 3.06 (t, J=6Hz, 2H).

4-[2-(1-Benzylimidazol-4-yl)ethyloxy]benzoic acid (3-6)

- 5 A mixture of 3-5 (170 mg, 0.51 mmol), 1N NaOH (5 mL), and CH₃OH (10 mL) was stirred at ambient temperature for 20 h. The reaction mixture was cooled to 0°C, neutralized with 1N HCl (5 mL), and then concentrated. The solid was extracted with CHCl₃ and the combined extracts concentrated to give 3-6 as a gelatinous solid.
- 10 ¹H NMR (300 MHz, CD₃OD) δ 7.90 (d, J=9Hz, 2H), 7.67 (s, 1H), 7.40-7.20 (m, 5H), 6.95 (s, 1H), 6.88 (d, J=9Hz, 2H), 5.16 (s, 2H), 4.22 (t, J=6Hz, 2H), 2.99 (t, J=6Hz, 2H).

15 4-[2-(1-Benzyl-imidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine tert-butyl ester (3-7)

- A stirred mixture of 3-6 (147 mg, 0.46 mmol), HOBT (94 mg, 0.61 mmol), 2-1 (154 mg, 0.46 mmol), NMM (100 μL, 0.91 mmol), and DMF (1.2 mL) at 0°C was treated with EDC (118 mg, 0.61 mmol) followed by removal of the cooling bath. The reaction pH was
- 20 adjusted to 8 by addition of more NMM. After 20 h the reaction mixture was concentrated and the residue purified by to a flash chromatography column (silica, 9/0.5/0.5 CH₂Cl₂/CH₃OH/AcOH) to give 3-7 as a yellow solid after azeotropic removal of residual AcOH with toluene. R_f 0.48 (silica, 9/0.5/0.5 CH₂Cl₂/CH₃OH/AcOH).
- 25 ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, J=9Hz, 2H), 7.80-7.10 (m, 11H), 6.92 (d, J=9Hz, 2H), 6.75 (s, 1H), 6.58 (m, 1H), 5.67 (m, 1H), 5.06 (s, 2H), 4.29 (t, J=6Hz, 2H), 3.90 (m, 2H), 3.56 (m, 1H), 3.06 (t, J=6Hz, 2H), 1.29 (s, 9H).

30 4-[2-(1-Benzylimidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine (3-8)

 A solution of 3-7 (252 mg, 0.42 mmol), TFA (3 mL) and CH₂Cl₂ (10 mL) was stirred at ambient temperature for 3 h, followed by concentration. Flash chromatography (silica, 9:0.5:0.5 ethanol/

- 66 -

NH₄OH/H₂O (2x)) gave 3-8 as a viscous gum. R_f 0.08 (silica, 9:0.5:0.5 ethanol/NH₄OH/H₂O).

¹H NMR (300 MHz, CD₃OD) δ 7.99 (s, 1H), 7.84 (d, 2H), 7.72 (d, 2H), 7.40-7.20 (m, 8H), 7.06 (s, 1H), 6.92 (d, J=9Hz, 2H), 5.22 (s, 2H), 4.24 (t, J=6Hz, 2H), 3.86 (m, 1H), 3.68 (dd, 1H), 3.53 (dd, 1H), 3.03 (t, J=6Hz, 2H).

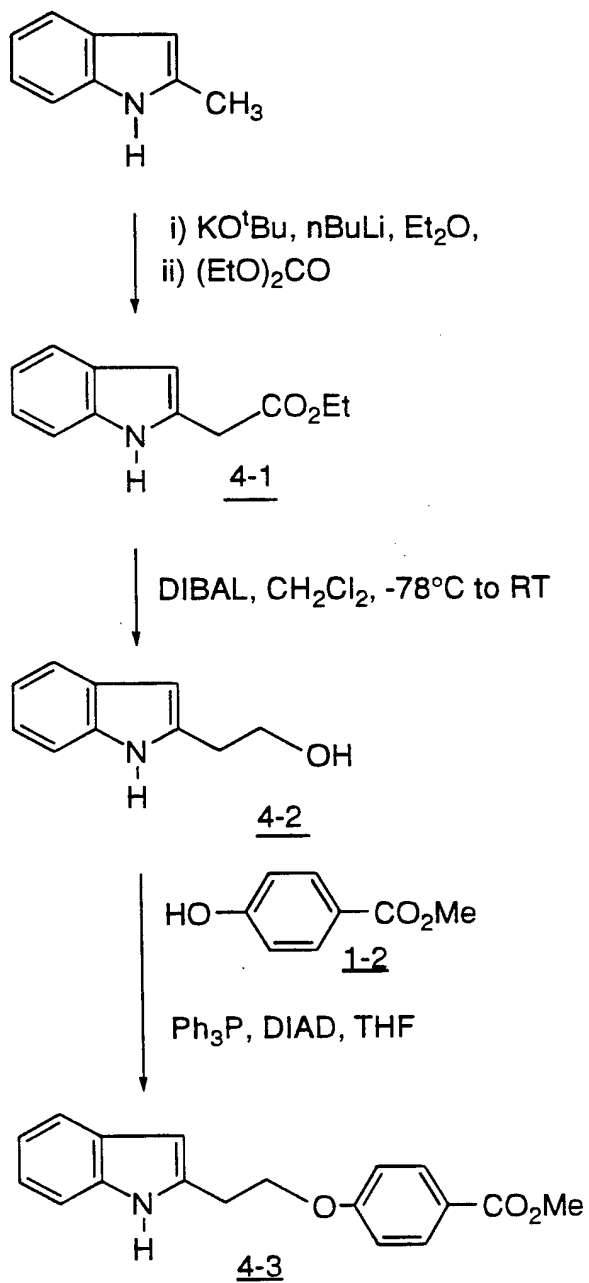
4-[2-(Imidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (3-9)

10 A mixture of 3-8 (94 mg, 0.17 mmol), 10% Pd/C (94 mg), and 4.4% formic acid/CH₃OH was stirred at ambient temperature under a hydrogen atmosphere (1 atm) for 72 h. The reaction mixture was filtered through a celite pad and the filtrate concentrated. Flash chromatography (silica, 5/3/0.5 CH₂Cl₂/CH₃OH/32% AcOH; then
15 10/1/1 ethanol/NH₄OH/H₂O) gave 3-9 as a colorless solid. R_f 0.33 (silica, 5/3/0.5 CH₂Cl₂/CH₃OH/32% AcOH).

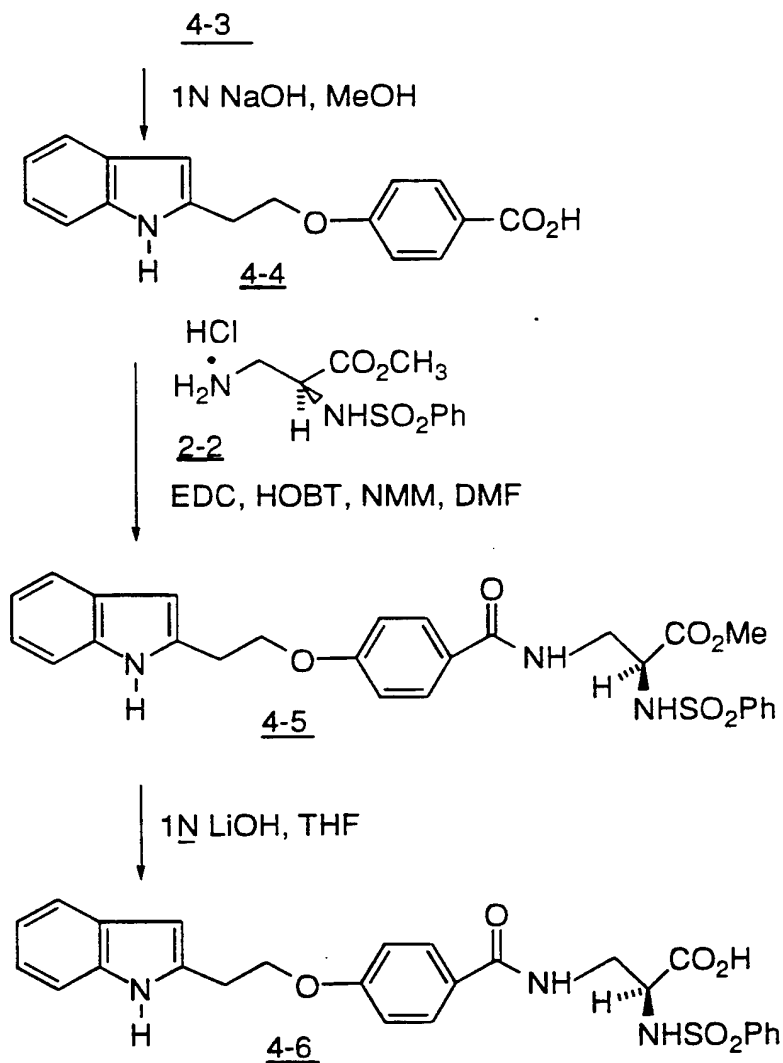
¹H NMR (400 MHz, CD₃OD) δ 7.85 (m, 3H), 7.77 (d, J=9Hz, 2H), 7.50 (m, 3H), 7.03 (s, 1H), 6.97 (d, J=9Hz, 2H), 4.28 (t, J=6Hz, 2H), 3.77 (m, 1H), 3.67 (dd, 1H), 3.54 (dd, 1H), 3.11 (t, J=6Hz, 2H).

20

- 67 -

SCHEME 4

- 68 -

SCHEME 4 (CONT'D)Ethyl Indol-2-ylacetate (4-1)

- 2-Methylindole (1.7 g, 13 mmol) in 130 mL Et₂O was treated with nBuLi (1.6 M in hexane, 24.4 mL, 39 mmol) and KO^tBu (1.0 M in THF, 26 mL, 26 mmol) at RT for 40 min, then diethylcarbonate (3.15 mL, 26 mmol) was added. After 1 h the reaction was quenched with water, adjusted to pH 7 with 6N HCl, extracted with EtOAc, then the organic layer was washed with water and brine, dried

- 69 -

(MgSO₄), and concentrated. Flash chromatography (silica 10% then 20% EtOAc/hexane) provided 4-1 as a brown oil.

R_f 0.33 (silica, 20% EtOAc/hexane).

¹H NMR (300 MHz, CDCl₃) δ 8.67 (br s, 1H), 7.55 (dd, J=8,1 Hz, 1H),
5 7.35 (dd, J=8, 1 Hz, 1H), 7.20-7.05 (m, 2H), 6.35 (m, 1H), 4.21 (q, J=7
Hz, 2H), 3.83 (s, 2H), 1.30 (t, J=7 Hz, 3H).

2-(Indol-2-yl)ethanol (4-2)

Ester 4-1 (0.54 g, 2.6 mmol) was dissolved in 13 mL
10 CH₂Cl₂ at -78°, and DIBAL (1 M in CH₂Cl₂, 5.8 ml, 5.8 mmol) was
added dropwise. The mixture was stirred at -78° for 15 min then
warmed to RT for 30 min and quenched in sat. aqueous Na/K tartrate.
This solution was extracted with EtOAc. The organic layer was washed
with brine, dried (Na₂SO₄), and concentrated. Flash chromatography
15 (silica 50% EtOAc/hexane) provided 4-2 as a brown oil.

R_f 0.38 (silica, 50% EtOAc/hexane).

¹H NMR (300 MHz, CDCl₃) δ 8.43 (br s, 1H), 7.54 (dd, J=8, 1 Hz,
1H), 7.32 (dd, J=8, 1 Hz, 1H), 7.20-7.05 (m, 2H), 6.29 (m, 1H), 3.9 (q,
20 J=5 Hz, 2H), 3.02 (t, J=5 Hz, 2H).

Methyl 4-[2-(Indol-2-yl)ethoxy]benzoate (4-3)

Alcohol 4-2 (136 mg, 0.84 mmol), phenol 1-2 (128 mg,
0.84 mmol) and Ph₃P (277 mg, 1.06 mmol) were combined in 8 mL
THF, and a solution of DIAD (0.22 mL, 1.1 mmol) in 5 mL THF was
25 added dropwise during 1.5 h. After 2.5 h the mixture was diluted with
EtOAc, washed with water/brine, 1N NaOH, and brine, dried (MgSO₄),
and concentrated. Flash chromatography (silica 15% EtOAc/hexane)
provided 4-3 as an oil.

R_f 0.14 (silica, 15% EtOAc/hexane).

30 ¹H NMR (300 MHz, CDCl₃) δ 8.25 (br s, 1H), 8.01 (dd, J=9 Hz, 2H),
7.55 (dd, J=8, 1 Hz, 1H), 7.34 (dd, J=8, 1 Hz, 1H), 7.20-7.05 (m, 2H),
6.97 (d, J=9 Hz, 2H), 6.34 (m, 1H), 4.34 (t, J=6 Hz, 2H), 3.89 (s, 3H),
3.28 (t, J=6 Hz, 2H).

- 70 -

4-[2-(Indol-2-yl)ethyloxy]benzoic acid (4-4)

Ester 4-3 (150 mg, 0.51 mmol) and 1N NaOH (1.3 mL, 1.3 mmol) were combined in 10 mL MeOH. After 16 h additional 1N NaOH (5 mL, 5 mmol) was added, and 7 h later, 5 mL more 1N NaOH.

- 5 After a total of 2 d the mixture was heated at 50° for 1 h, then concentrated, redissolved in H₂O, washed with EtOAc, and the pH of the aqueous layer was adjusted to 1 with 20% KHSO₄. This was extracted with EtOAc, and this organic layer was washed with brine, dried (MgSO₄) and concentrated, providing 4-4 as a gray solid.

- 10 R_f 0.48 (silica, EtOAc).

¹H NMR (300 MHz, CD₃OD) δ 7.96 (d, J=9 Hz, 2H), 7.42 (ds J=8 Hz, 1H), 7.29 (dd, J=8, 1 Hz, 1H), 7.02 (d, J=9 Hz, 2H), 7.03-6.93 (m, 2H), 6.27 (s, 1H), 4.37 (t, J=7 Hz, 2H), 3.25 (t, J=7 Hz, 2H).

- 15 4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine methyl ester (4-5)

Acid 4-4 (100 mg, 0.36 mmol), amine 2-2 (105 mg, 0.36 mmol), EDC (88 mg, 0.46 mmol), HOBT (62 mg, 0.46 mmol) and NMM (137 μL, 1.2 mmol) were combined in 2 mL DMF. After 16 h the mixture was diluted with EtOAc, washed with water, sat. NaHCO₃, 20 5% KHSO₄, and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 65% EtOAc/hexane) provided 4-5 as an oil. R_f 0.32 (silica, 65% EtOAc/hexane).

- 25 ¹H NMR (300 MHz, CDCl₃) δ 8.41 (br s, 1H), 7.83 (d, J=7 Hz, 2H), 7.74 (d, J=9 Hz, 2H), 7.60-7.43 (m, 4H), 7.34 (dd, J=8, 1 Hz, 1H), 7.20-7.02 (m, 2H), 6.93 (d, J=9 Hz, 2H), 6.72 (br t, 1H) 6.34 (m, 1H), 5.87 (d, J=8 Hz, 1H), 4.28 (t, J=6 Hz, 2H), 4.05 (m, 1H), 3.86 (m 1H), 3.67 (m, 1H), 3.60 (s, 3H), 3.26 (t, J=6 Hz, 2H).

- 30 4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (4-6)

Ester 4-5 (147 mg, 0.28 mmol), and 1 N LiOH (0.70 mL, 0.70 mmol), were combined in 3 mL THF. After 16 h the mixture was

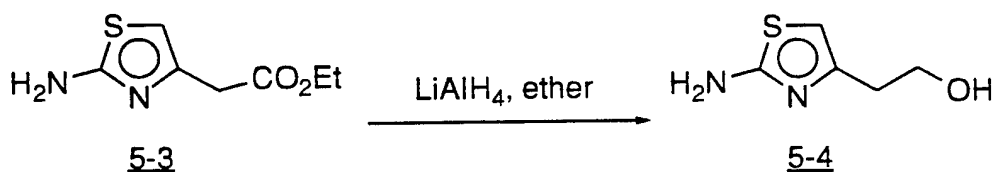
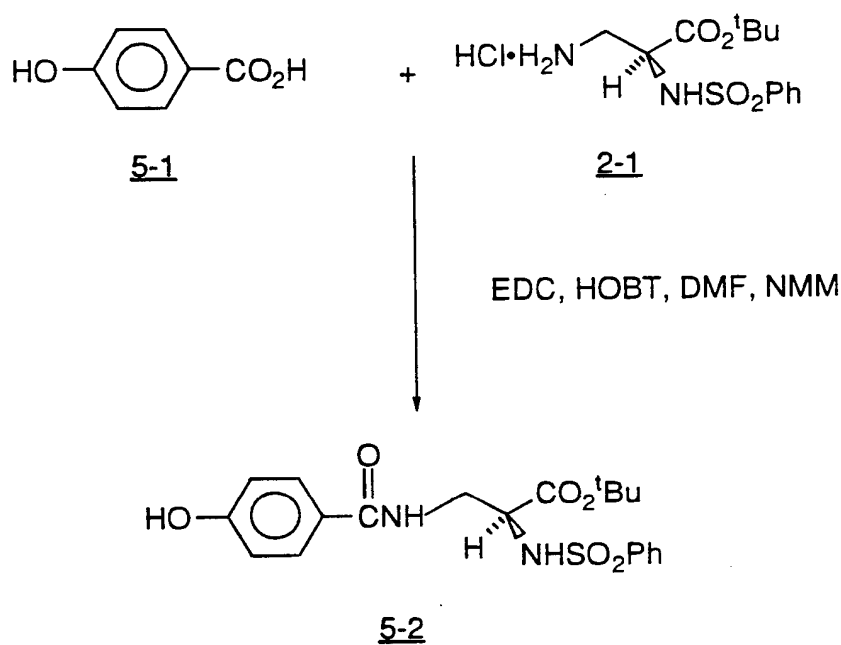
- 71 -

concentrated and purified by flash chromatography (silica, 33:20:1:1 EtOAc/EtOH/NH₄OH/H₂O) providing 4-6 as a white solid.

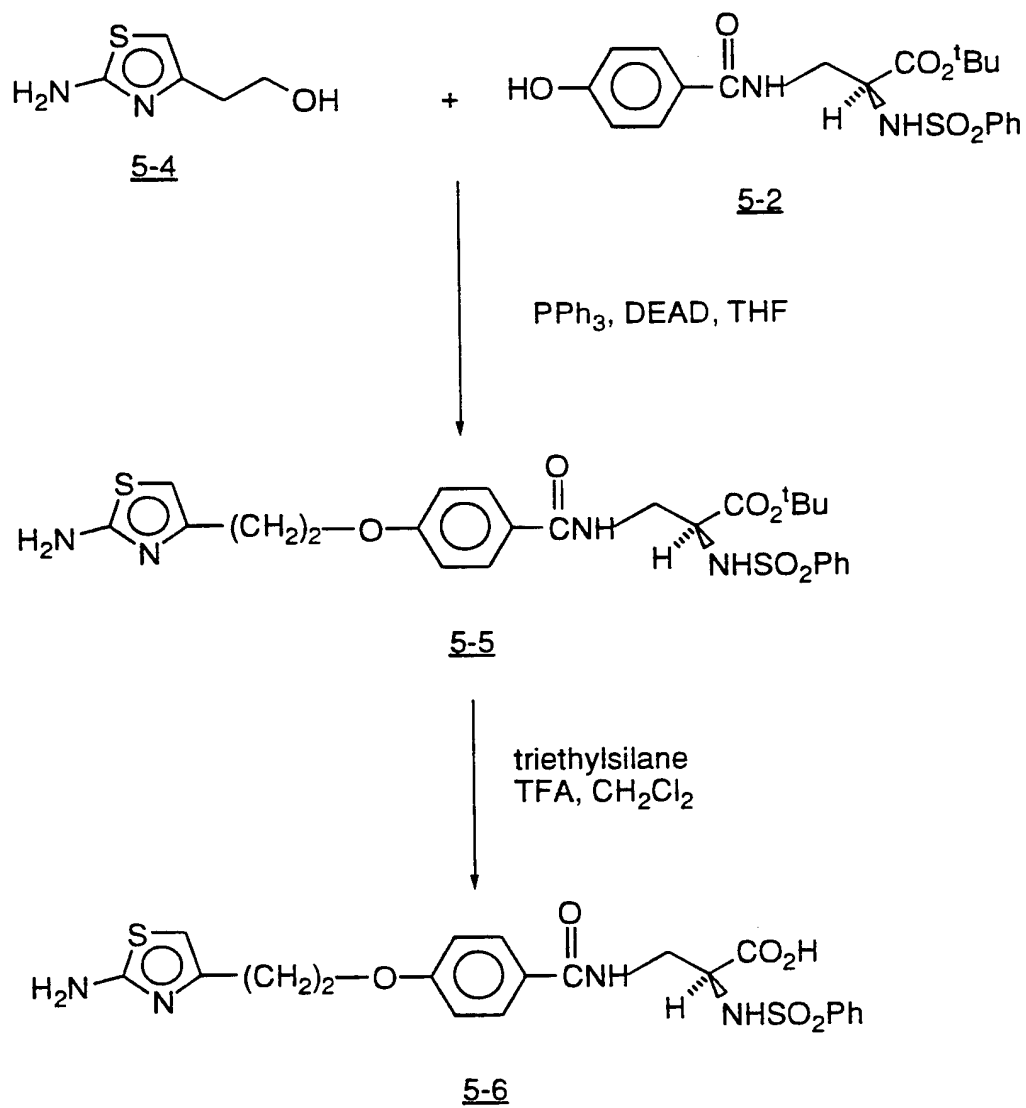
R_f 0.33 (silica, 33:20:1:1 EtOAc/EtOH/NH₄OH/H₂O).

- ¹H NMR (300 MHz, DMSO) δ 8.46 (br s, 1H), 7.77 (d, J=7 Hz, 2H),
 5 7.71 (d, J=9 Hz, 2H), 7.60-7.46 (m, 3H), 7.41 (d, J=8 Hz, 1H), 7.29 (d, J=8 Hz, 1H), 7.02 (d, J=9 Hz, 2H), 7.02-6.86 (m, 4H), 6.26 (br s, 1H), 4.35 (t, J=7 Hz, 2H), 3.60-3.20 (m), 3.19 (t, J=7 Hz, 2H).

SCHEME 5



- 72 -

SCHEME 5 (CONT'D)

- 73 -

4-Hydroxybenzoyl-2(S)-phenylsulfonylamino- β -alanine tert-butyl ester
(5-2)

To a stirred solution of 5-1 (0.41 g, 2.9 mmol; Aldrich),
2-1 (1.0 g, 2.9 mmol), HOBT (0.52 g, 3.9 mmol) NMM (0.65 mL, 5.9
5 mmol), and DMF (15 mL) at 0°C was added EDC (0.74 g, 3.9 mmol)
followed by removal of the cooling bath. After 20 h, the reaction
mixture was diluted with EtOAc and then washed with H₂O (2x), sat.
NaHCO₃, 5% KHSO₄ and brine, dried (MgSO₄), filtered and
concentrated. Flash chromatography (silica, 60% to 80%
10 EtOAc/hexanes), then redissolving in EtOAc, washing with water (2x)
and brine, drying, filtering and concentrating gave 5-2 as a white foam.
R_f 0.38 (silica, 60% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 7.86 (m, 2H), 7.72 (d, J=9Hz, 2H), 7.53
(m, 3H), 6.87 (d, J=9Hz, 2H), 6.62 (m, 1H), 5.63 (d, J=7Hz, 1H), 5.42
15 (m, 1H), 3.90 (m, 2H), 3.55 (m, 1H), 1.29 (s, 9H).

2-(2-Aminothiazol-4-yl)ethanol (5-4)

To a stirring suspension of 5-3 (2.0 g, 10.7 mmol; Fluka)
in ether (54 mL) at ambient temperature was added LiAlH₄ (16.1 mL,
20 16.1 mmol; 1M/THF) dropwise. After complete addition, the reaction
mixture was stirred for 30 min and then quenched by sequential
addition of H₂O (0.61 mL), 15% NaOH (0.61 mL), and H₂O (1.83
mL). The reaction mixture was filtered through a celite pad and the
filtrate concentrated to give 5-4 as a brown oil.

25 R_f 0.26 (silica, 5:1:1 CH₂Cl₂/CH₃OH/AcOH).

¹H NMR (400 MHz, DMSO) δ 6.81 (s, 1H), 3.76 (t, J=6Hz, 2H), 2.88
(t, J=6Hz, 2H).

4-[2-(2-Aminothiazol-4-yl)ethoxy]benzoyl-2(S)-phenylsulfonylamino-
30 β -alanine tert-butyl ester (5-5)

To a stirred solution of 5-2 (0.14 g, 0.32 mmol) and PPh₃
(0.11g, 0.41 mmol) in THF (2 mL) at ambient temperature was added a
solution of 5-4 (56 μ g, 0.39 mmol) DEAD (67 μ L, 0.42 mmol) in THF
(2 mL) dropwise over a 15 min period. After 72 h, the reaction

- 74 -

mixture was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. After two flash columns: silica, 85% EtOAc/hexanes; silica, 5% to 30% isopropanol/CHCl₃, 5-5 was obtained as a yellow oil. R_f 0.19

5 (silica, 85% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.86 (m, 2H), 7.73 (d, J=9Hz, 2H), 7.52 (m, 3H), 6.92 (d, J=9Hz, 2H), 6.67 (m, 1H), 6.22 (s, 1H), 5.81 (m, 1H), 5.5 (m, 2H), 4.24 (t, J=6Hz, 2H), 3.90 (m, 2H), 3.56 (m, 1H), 3.02 (t, J=6Hz, 2H), 1.28 (s, 9H).

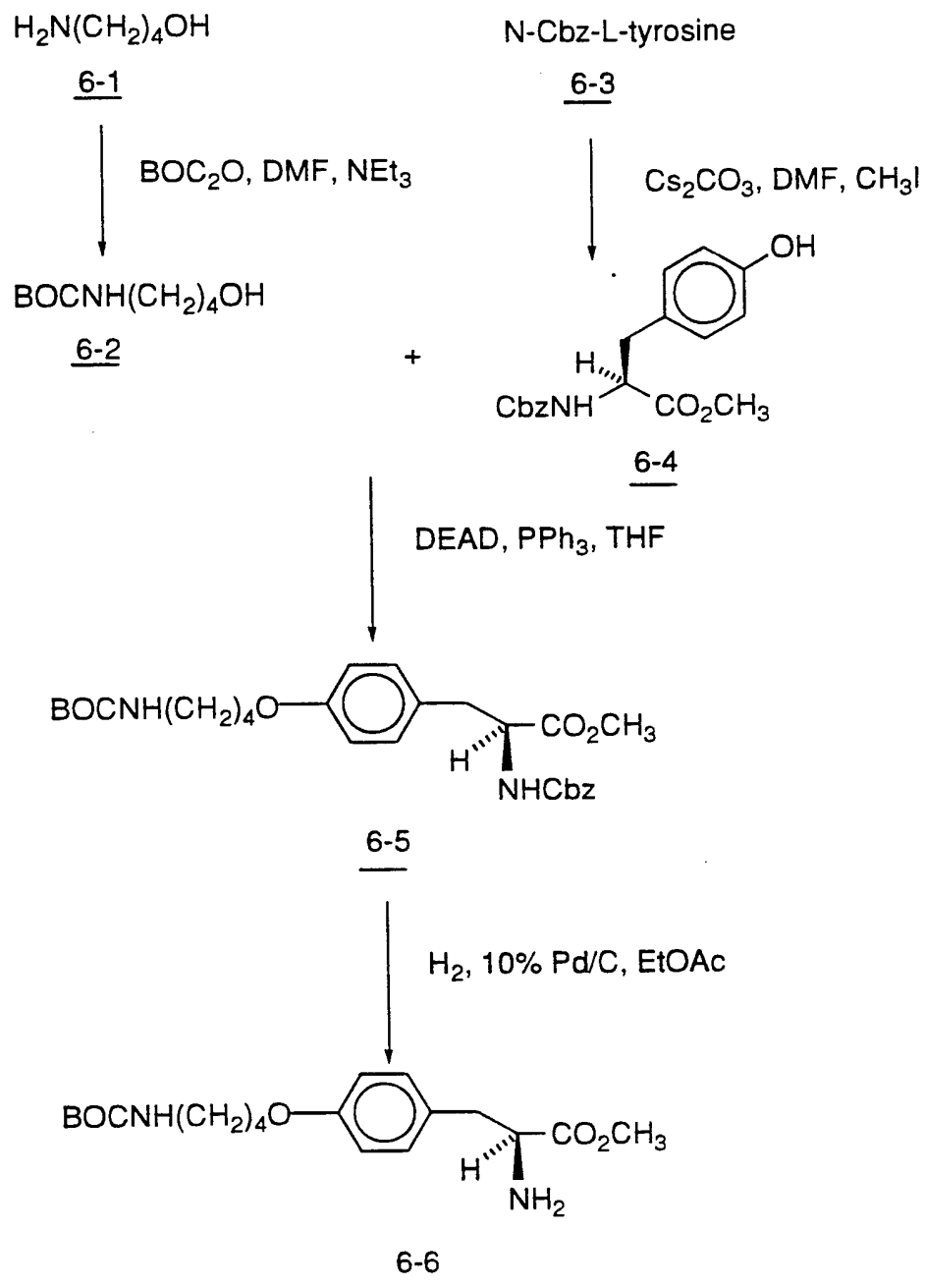
10

4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (5-6)

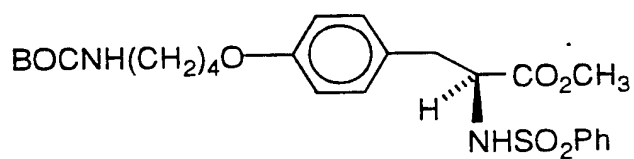
15 A stirred solution of 5-5 (33 mg, 60 μmol), CH₂Cl₂ (0.5 mL), and triethylsilane (24 μL, 0.15 mmol) at ambient temperature was treated with TFA (0.5 mL). After 4 h, the solution was concentrated and the residual TFA removed azeotropically with toluene. Flash chromatography (silica, 10:0.1:0.1 ethanol/NH₄OH/H₂O) gave 5-6 as a white solid.

20 ¹H NMR (400 MHz, D₂O + DCl) δ 7.49 (m, 2H), 7.30 (d, J=9Hz, 2H), 7.08 (m, 3H), 6.73 (d, J=9Hz, 2H), 4.11 (t, 2H), 3.97 (m, 1H), 3.50 (m, 1H), 3.38 (m, 1H), 3.20 (m, 1H) 2.82 (m, 2H).

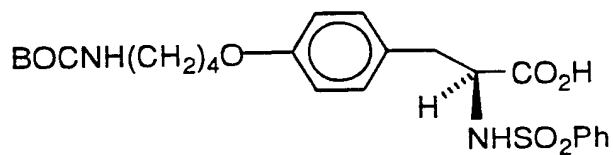
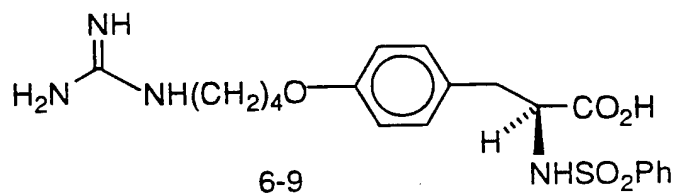
- 75 -

SCHEME 6

- 76 -

SCHEME 6 (CONT'D)6-6CH₂Cl₂, pyridine, PhSO₂Cl6-7

1N NaOH, ethanol

6-8a) TFA/CH₂Cl₂b) DMF/H₂O, N(i-Pr)₂Et, DPFN6-9

- 77 -

4-N-BOC-Aminobutanol (6-2)

To a stirred solution of 6-1 (Aldrich) (5.0 g, 56 mmol), NEt₃ (11.7 mL, 84 mmol), and DMF (150 mL) at 0°C was added BOC₂O (14.7 g, 67 mmol) followed by removal of the cooling bath.

- 5 After 1.0 h, the solution was diluted with EtOAc and then washed with 10% KHSO₄ and brine, dried (MgSO₄) and concentrated to give 6-2 as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 3.68 (m, 2H), 3.15 (m, 2H), 1.60 (m, 4H), 1.47 (s, 9H).

10

N-Cbz-L-Tyrosine methyl ester (6-4)

A suspension of Cs₂CO₃ (0.65 g, 2.0 mmol), N-Cbz-L-tyrosine (1.3 g, 4.0 mmol; Bachem) and DMF (40 mL) at ambient temperature was treated with methyl iodide (0.5 mL, 4.0 mmol). After

15 2.0 h the reaction mixture was diluted with EtOAc and then washed with H₂O and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 25% EtOAc/hexanes) gave 6-4 as a white solid. R_f 0.53 (silica, 50% EtOAc/hexanes).

- 20 Methyl 2(S)-(N-Benzyloxycarbonylamino)-3-[4-(4-N-Boc-amino-butyloxy)phenyl]propionate (6-5)

To a stirred solution of 6-4 (500 mg, 1.5 mmol), PPh₃ (0.5 g, 1.9 mmol) and THF (10 mL) was added a solution of 6-2 (430 mg, 2.3 mmol), DEAD (326 mg, 1.9 mmol), and THF (10 mL)

- 25 dropwise over a 30 min period. After 2.0 h the solution was diluted with EtOAc and then washed with H₂O, 1N NaOH, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 25% EtOAc/hexanes) gave 6-5 as a white solid. R_f 0.50 (silica, 50% EtOAc/hexanes).

- 30 ¹H NMR (300 MHz, CD₃OD) δ 7.22 (m, 5H), 7.02 (d, J=9Hz, 2H), 6.72 (d, J=9Hz, 2H), 4.97 (m, 2H), 4.34 (m, 1H), 3.89 (m, 2H), 3.63 (s, 3H), 3.02 (m, 2H), 3.01 (m, 1H), 2.81 (m, 1H), 1.73 (m, 2H), 1.62 (m, 2H), 1.47 (s, 9H).

- 78 -

Methyl 2(S)-amino-3-[4-(4-N-Boc-aminobutyloxy)phenyl]propionate (6-6)

A mixture of 6-5 (500 mg, 0.99 mmol), 10% Pd/C (250 mg), and EtOAc (5 mL) was stirred under a hydrogen atmosphere (1 atm) at ambient temperature for 1.0 h. The reaction mixture was then filtered through a celite pad and the filtrate concentrated to give 6-6 as a yellow solid. R_f 0.36 (silica, 10:1:1 CH₂Cl₂/CH₃OH/AcOH).
¹H NMR (300 MHz, CD₃OD) δ 7.02 (d, J=9Hz, 2H), 6.80 (d, J=9Hz, 2H), 3.90 (m, 2H), 3.63 (s, 3H), 3.03 (m, 2H), 2.85 (m, 2H), 1.73 (m, 2H), 1.62 (m, 2H), 1.47 (s, 9H).

Methyl 2(S)-phenylsulfonylamino-3-[4-(4-N-Boc-aminobutyloxy)-phenyl]propionate (6-7)

To a stirred solution of 6-6 (350 mg, 0.95 mmol), CH₂Cl₂ (5 mL), and pyridine (229 μL, 3.0 mmol) at 0°C was added phenylsulfonyl chloride (145 μL, 1.2 mmol), followed by removal of the cooling bath. After 20 h the reaction mixture was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 30% EtOAc/hexanes) gave 6-7 as a colorless oil. R_f 0.31 (silica, 30% EtOAc/hexanes).
¹H NMR (300 MHz, CD₃OD) δ 7.25-7.00 (m, 5H), 6.52 (d, J=9Hz, 2H), 6.30 (d, J=9Hz, 2H), 3.58 (m, 1H), 3.50 (t, 2H), 2.97 (s, 3H), 2.67 (t, 2H), 2.45 (dd, 1H), 2.32 (dd, 1H), 1.32 (m, 2H), 1.21 (m, 2H), 1.01 (s, 9H).

2(S)-Phenylsulfonylamino-3-[4-(4-N-Boc-aminobutyloxy)phenyl]-propionic acid (6-8)

A solution of 6-7 (350 mg, 0.69 mmol), 1N NaOH (1.5 mL), and ethanol (3.5 mL) was stirred at ambient temperature for 1.0 h. The solution was then acidified with 10% KHSO₄ and extracted with EtOAc. The EtOAc portion was washed with brine, dried (MgSO₄) and concentrated to give 6-8 as a white solid. R_f 0.71 (silica, 10:1:1 CH₂Cl₂/CH₃OH/AcOH).

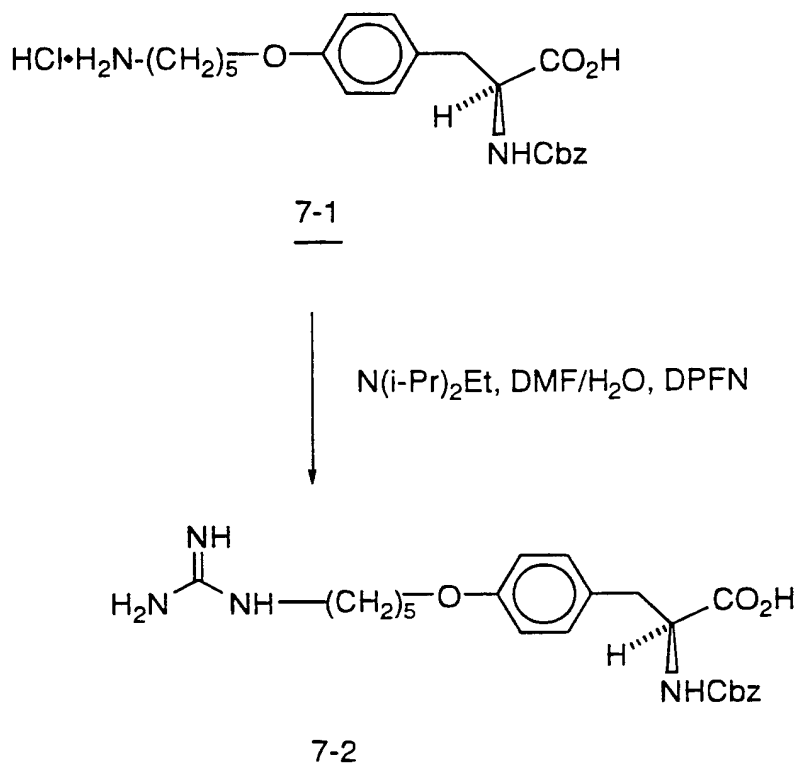
- 79 -

¹H NMR (300 MHz, CD₃OD) δ 7.60-7.30 (m, 5H), 6.92 (d, J=9Hz, 2H), 6.63 (d, J=9Hz, 2H), 3.87 (m, 3H), 3.02 (t, 2H), 2.88 (dd, 1H), 2.68 (dd, 1H), 1.70 (m, 2H), 1.58 (m, 2H), 1.45 (s, 9H).

5 2(S)-Phenylsulfonylamino-3-[4-(4-guanidobutyloxy)phenyl]propionic acid (6-9)

- A solution of 6-8 (300 mg, 0.60 mmol), TFA (3 mL), and CH₂Cl₂ (3 mL) was stirred at ambient temperature for 1.0 h. The solution was concentrated followed by azeotropic removal of the residual TFA with toluene. The residue was dissolved in 1:1 DMF/H₂O (3.0 mL) and then treated with N(i-Pr)₂Et (316 μL, 1.8 mmol) and DPFN (1.33 mg, 0.91 mmol). After heating at 40°C for 2.0 h the reaction mixture was concentrated. Flash chromatography (silica, 10/0.1/0.1 to 10/1/1 ethanol/NH₄OH/H₂O) gave 6-9 as a white solid.
- 10
- 15 R_f 0.33 (silica, 10:1:1 ethanol/NH₄OH/H₂O).
¹H NMR (400 MHz, CD₃OD) δ 7.75-7.45 (m, 5H), 7.06 (d, J=9Hz, 2H), 6.78 (d, J=9Hz, 2H), 4.02 (m, 3H), 3.30 (m, 2H), 3.00 (dd, 1H), 2.79 (dd, 1H), 1.77 (m, 4H).

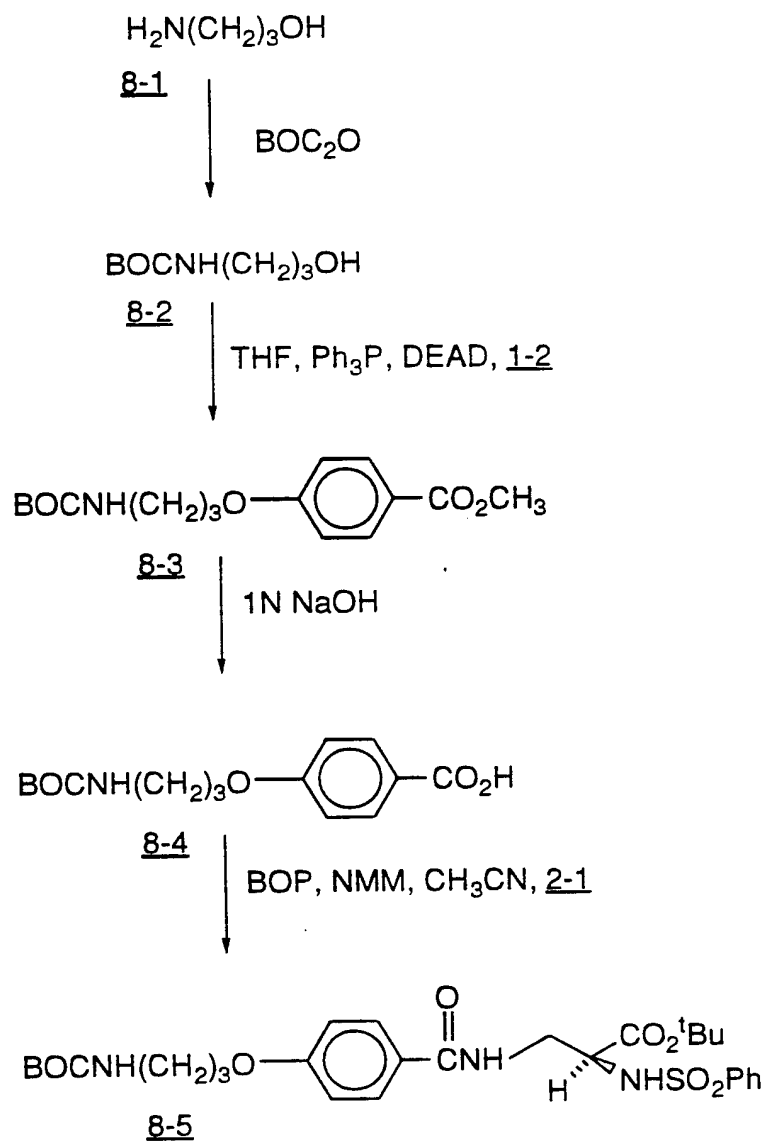
- 80 -

SCHEME 7

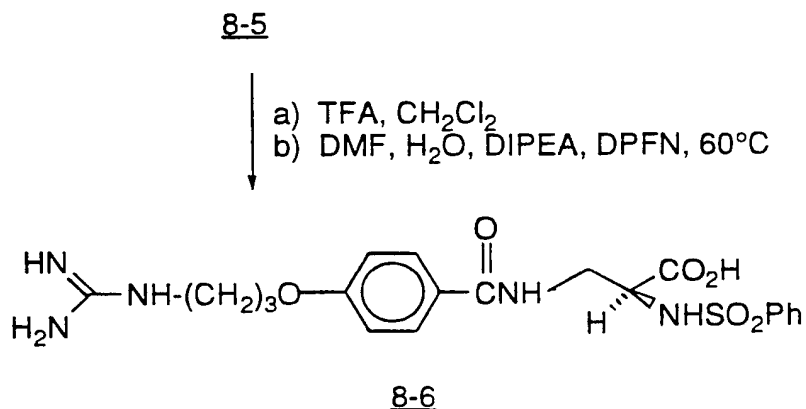
5 2-S-(N-Benzyloxycarbonylamino)-3-[4-(5-guanidopentyloxy)-phenyl]propionic acid (7-2)

- A stirred solution of 7-1 (225 mg, 0.56 mmol; for preparation see Duggan, et al, European Publication 478362), diisopropylethylamine (0.6 mL, 3.4 mmol), DMF (4 mL), and H₂O (1 mL) was treated with 3,5-dimethyl-1-pyrazolylformaminidium nitrate (DPFN) (0.68 g, 3.4 mmol) then heated at 60°C for 20 h. Concentration followed by flash chromatography (silica, ethanol/NH₄OH/H₂O 10:0.3:0.3) gave 7-2 as a white solid. R_f 0.59 (silica, 10:1:1 ethanol/NH₄OH/H₂O).
- 15 ¹H NMR (400 MHz, CD₃OD) δ 7.30 (m, 5H), 7.07 (d, 2H), 6.73 (d, 2H), 5.07 (d, 1H), 4.98 (d, 1H), 4.21 (m, 1H), 3.96 (t, 2H), 3.16 (t, 2H), 3.08 (dd, 1H), 2.89 (dd, 1H), 1.80-1.50 (m, 6H).

- 81 -

SCHEME 8

- 82 -

SCHEME 8 (CONT'D)5 3-(N-BOC-Amino)propanol (8-2)

To a stirred solution of 3-aminopropanol 8-1 (Aldrich) (15 g, 0.2 mol), NEt₃ (42 mL, 0.3 mol) and DMF (400 mL) at 0°C was added BOC₂O (52 g, 0.24 mol). After stirring at 0°C for 6 h the reaction mixture was diluted with ether and then washed with H₂O (2x),
 10 sat. NaHCO₃, 5% KHSO₄ and brine, dried (MgSO₄) and concentrated to give 8-2 as a colorless oil.
 TLC R_f 0.42 (silica, 20% EtOAc/hexanes);
¹H NMR (300 MHz, CDCl₃) δ 3.68 (t, J=7 Hz, 2H), 3.30 (t, J=7 Hz, 2H), 1.69 (m, 2H), 1.45 (s, 9H).

15

. Methyl 4-(3-N-BOC-Aminopropoxy)benzoate (8-3)

Following the procedure for coupling 1-1 to 1-2, 8-2 (13.8 g, 79 mmol) was coupled to 1-2 (8.0 g, 53 mmol) to give 8-3 as a yellow oil after flash chromatography (silica, 5% EtOAc/hexanes).
 20 TLC R_f=0.38 (silica, 20% EtOAc/hexanes);
¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, J=9 Hz, 2H), 6.92 (d, J=9 Hz, 2H), 4.70 (m, 1H), 4.08 (m, 2H), 3.88 (s, 3H), 3.33 (m, 2H), 2.00 (m, 2H), 1.46 (s, 9H).

- 83 -

4-(3-N-BOC-Aminopropoxy)benzoic acid (8-4)

A solution of 8-3 (16 g, 52 mmol), 1N NaOH (100 mL), and ethanol (150 mL) was stirred at ambient temperature for 20 h. The reaction mixture was acidified with 10% KHSO₄ and then extracted with EtOAc. The EtOAc portion was washed with brine, dried (MgSO₄) and concentrated. Trituration of the residue with ether gave 8-4 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 7.87 (d, J=9 Hz, 2H), 6.88 (d, J=9 Hz, 2H), 3.98 (t, J=6 Hz, 2H), 3.15 (t, J=6 Hz, 2H), 1.86 (m, 2H), 1.33 (s, 9H).

4-[3-(N-BOC-Amino)propoxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine tert-butyl ester (8-5)

Following the procedure for coupling 1-4 to 2-1, 8-4 (300 mg, 1.0 mmol) was coupled to 2-1 (372 mg, 1.2 mmol) to furnish 8-5 as a colorless oil after flash chromatography (silica, 50% EtOAc/hexanes).

TLC R_f 0.33 (silica, 50% EtOAc/hexanes);

¹H NMR (300 MHz, 10% CD₃OD/CDCl₃) δ 7.8 (m, 2H), 7.76 (d, J=9 Hz, 2H), 7.51 (m, 3H), 6.92 (d, J=9 Hz, 2H), 4.10 (m, 2H), 4.00-3.60 (m, 3H), 3.32 (m, 2H), 2.00 (m, 2H), 1.45 (s, 9H), 1.28 (s, 9H).

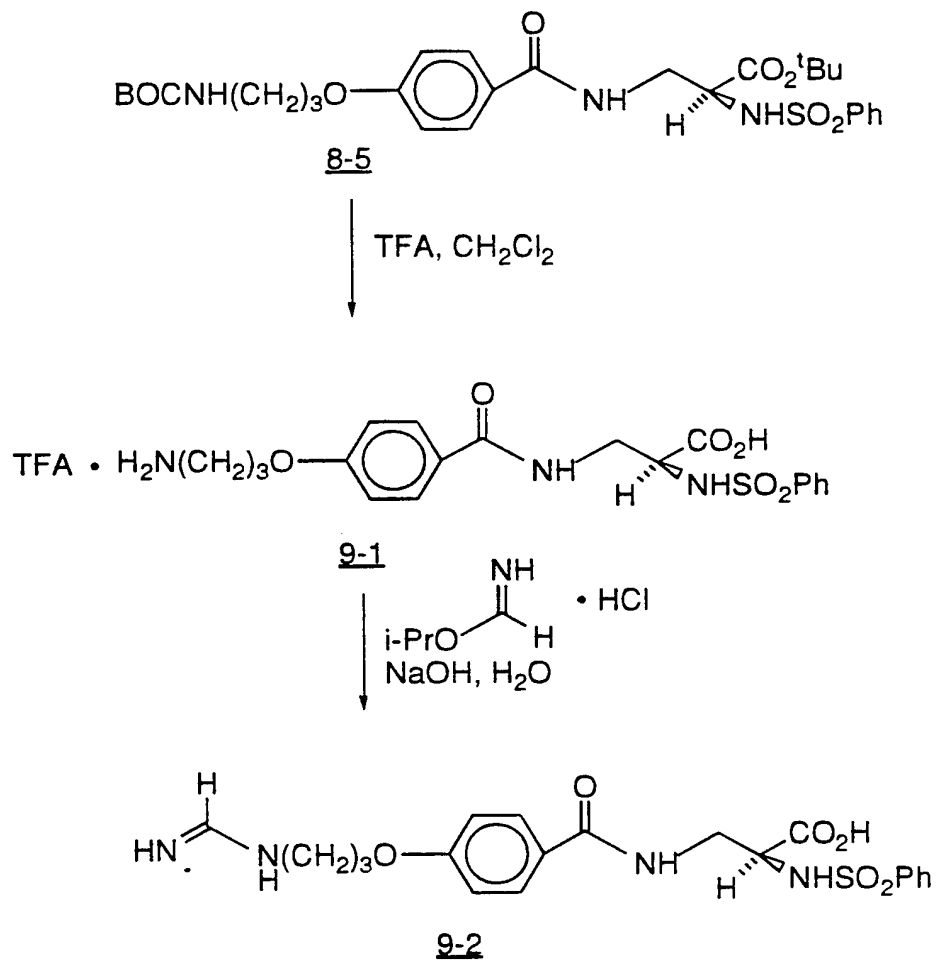
4-(3-Guanidopropoxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine (8-6)

Following the procedure for converting 2-3 to 2-4, 8-5 (300 mg, 0.55 mmol) furnished 8-6 as a white solid after flash chromatography (silica, 10:1:1 ethanol/H₂O/NH₄OH).

TLC R_f 0.28 (silica, 10:1:1 ethanol/H₂O/NH₄OH);

¹H NMR (400 MHz, D₂O) δ 7.65 (m, 2H), 7.43 (d, J=9 Hz, 2H), 7.24 (m, 3), 6.90 (d, J=9 Hz, 2H), 4.13 (m, 1H), 4.10 (m, 2H), 3.68 (m, 1H), 3.52 (m, 1H), 3.40-3.25 (m, 3H), 2.00 (m, 2H).

- 84 -

SCHEME 9

- 85 -

4-(3-Aminopropoxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine
trifluoroacetate (9-1)

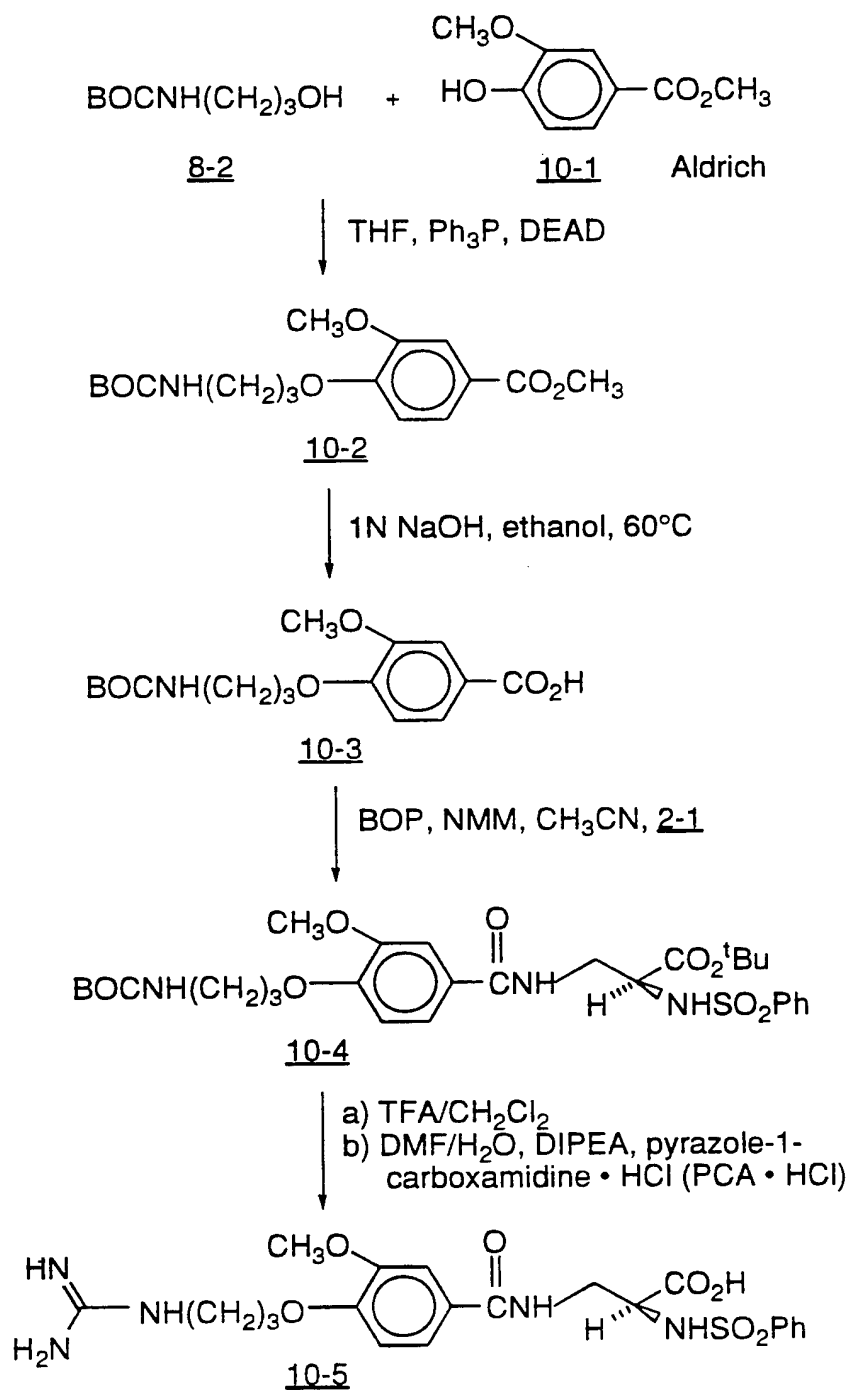
5 8-5 (497 mg, 1.04 mmol) in 5 mL CH₂Cl₂ was treated with
5 mL TFA at 0° for 30 min then RT for 10 min. Concentration
provided 9-1 as a yellow oil.
R_f 0.52 (silica, 10:1:1 ethanol/NH₄OH/H₂O).
¹H NMR (400 MHz, CD₃OD) δ 7.9-7.6 (m, 4H) 7.55-7.45 (m, 3H),
7.02 (d, 2H), 4.18 (t, 2H), 3.70 (m, 1H), 3.48 (m, 1H), 3.16 (t, 2H),
3.05, (m, 1H), 2.16 (qn, 2H).

10

4-[3-(Formamidino)propoxy]benzoyl-2(S)-phenylsulfonylamino- β -
alanine (9-2)

15 The TFA salt 9-1 (80 mg, 0.19 mmol) was dissolved in
water at 0° and the pH of the solution was adjusted to 9 by addition of
1N NaOH. Isopropyl formimidate hydrochloride (130 mg, 0.95 mmol)
was added in two portions 10 min apart maintaining pH 9 with
additional 1N NaOH. After 60 min at 0° the reaction was warmed to
RT for 90 min, then lyophilized. Preparative HPLC (C-18, 0.1% TFA
H₂O/CH₃CN) provided 9-2 as a white solid.
20 ¹H NMR (400 MHz, D₂O) 7.81 (s, 1H), 7.77 (d, J=7 Hz, 2H), 7.60 (d,
J= 9 Hz, 2H), 7.46-7.35 (m, 3H), 7.05 (d, J=9 Hz, 2H), 4.23 (t, J=6 Hz,
2H), 3.91 (dd, J=10, 4 Hz, 1H), 3.68 (dd, J=14, 4 Hz, 1H), 3.56 (t,
J=6Hz, 2H), 3.40 (dd, J=14, 10, 1H), 2.19 (qn, J=6 Hz, 2H).

- 86 -

SCHEME 10

- 87 -

Methyl 3-methoxy-4-(3-N-BOC-aminopropoxy)benzoate (10-2)

Following the procedure for coupling 1-1 to 1-2, 8-2 (2.8 g, 16.1 mmol) was coupled to 10-1 (Aldrich) (1.9 g, 10.7 mmol) to give 10-2 as a colorless oil after flash chromatography (silica, 20%

5 EtOAc/hexanes).

TLC R_f 0.18 (silica, 20% EtOAc/hexanes);

¹H NMR (300 MHz, CDCl₃) δ 7.70 (dd, J=9 and 2 Hz, 1H), 7.57 (d, J=2 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 5.52 (m, 1H), 4.17 (m, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 3.40 (m, 2H), 2.08 (m, 2H), 1.48 (s, 9H).

10

3-Methoxy-4-(3-N-BOC-aminopropoxy)benzoic acid (10-3)

A solution of 10-2 (3.5 g, 10.2 mmol), 1N NaOH (20 mL) and ethanol (30 mL) was heated at 60°C for 2.0 h. The cooled reaction mixture was acidified with 10% KHSO₄ and extracted with EtOAc.

15 The organic portion was washed with brine, dried (MgSO₄) and concentrated. The residue was triturated with Et₂O and filtered to give 10-3 as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.68 (dd, J=9, 2 Hz, 1H), 7.60 (d, J=2 Hz, 1H), 7.02 (d, J=9 Hz, 1H), 4.15 (m, 2H), 3.92 (s, 3H), 3.30 (m, 2H),
20 2.03 (m, 2H), 1.47 (s, 9H).

3-Methoxy-4-[3-(N-BOC-amino)propoxy]benzoyl-2(S)-phenyl-sulfonylamino-β-alaninetert-butyl ester (10-4)

Following the procedure for coupling 1-4 to 2-1, 10-3 (230 mg, 0.71 mmol) was coupled to 2-1 (215 mg, 0.71 mmol) to give 10-4 as a white solid after flash chromatography (silica, 50% EtOAc/hexanes).

TLC R_f 0.31 (silica, 50% EtOAc/hexanes);

¹H NMR (300 MHz, CD₃OD) δ 7.80-7.30 (m, 7H), 6.93 (d, J=9 Hz, 1H), 6.61 (m, 1H), 4.05 (m, 3H), 3.82 (s, 3H), 3.61 (m, 1H), 3.43 (m, 1H), 3.22 (m, 2H), 1.92 (m, 2H), 1.47 (s, 9H), 1.18 (s, 9H).

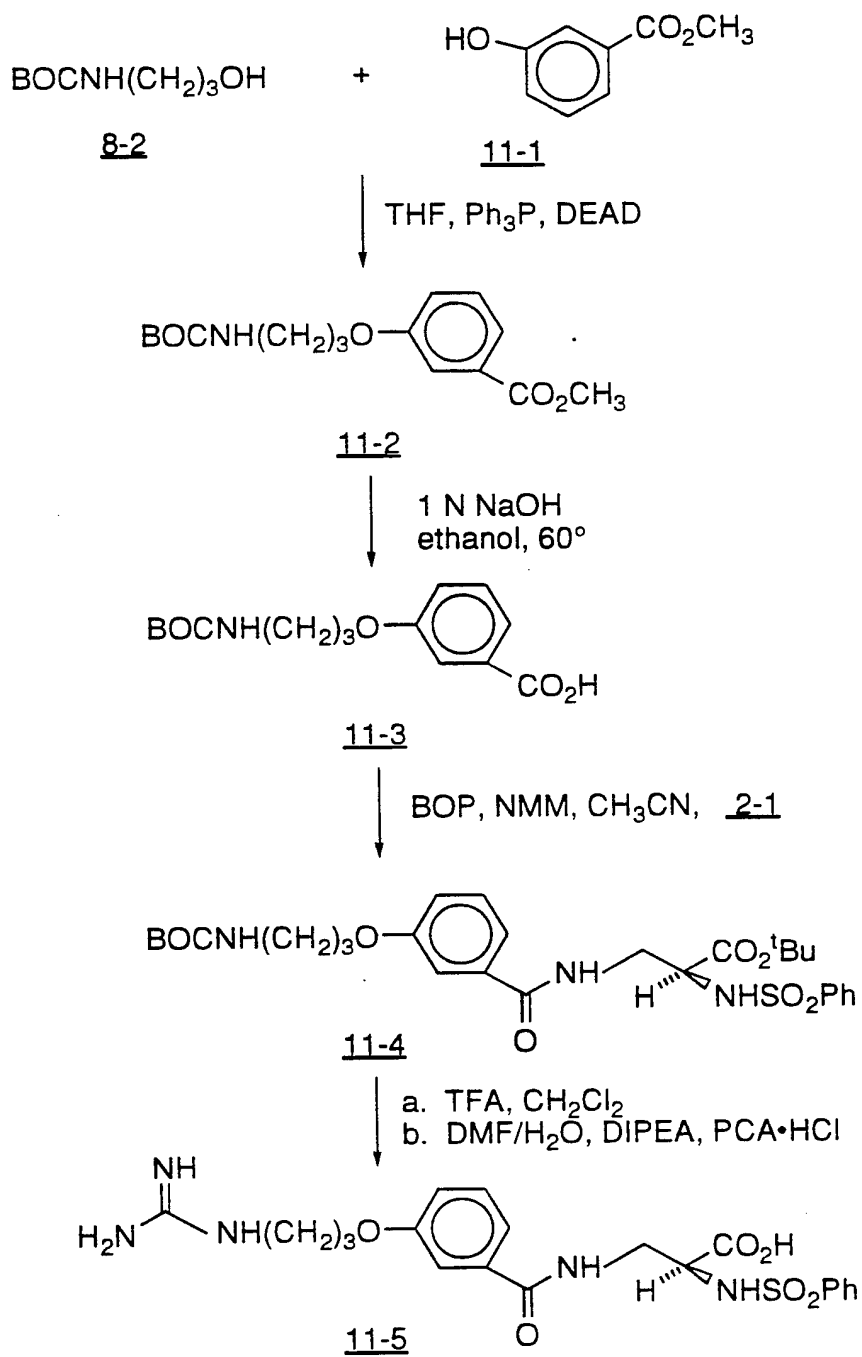
30

- 88 -

3-Methoxy-4-[3-guanidinopropoxy]benzoyl-2(S)-phenylsulfonyl-amino- β -alanine (10-5)

- A solution of 10-4 (350 mg, 0.61 mmol), TFA (3 mL) and CH₂Cl₂ (3 mL) was stirred at ambient temperature for 3.0 h. The
- 5 reaction mixture was concentrated and the residual TFA removed azeotropically with toluene. The residue was dissolved in DMF (1.5 mL) and H₂O (1.5 mL) and treated sequentially with DIPEA (317 μ L, 1.8 mmol) and pyrazole-1-carboxamide•HCl (PCA•HCl) (134 mg, 0.92 mmol). After 20 h at ambient temperature the reaction mixture
- 10 was concentrated. Flash chromatography (silica, 10:1:1 ethanol/NH₄OH/H₂O) gave 10-5 as a white solid.
- TLC R_f=0.18 (silica, 10:1:1 ethanol/NH₄OH/H₂O);
- ¹H NMR (400 MHz, CD₃OD) δ 7.90-7.40 (m, 7H), 7.08 (d, J=9 Hz, 1H), 4.27 (m, 1H), 4.22 (m, 2H), 3.96 (s, 3H), 3.82-3.45 (m, 4H), 2.15
- 15 (m, 2H).

- 89 -

SCHEME 11

- 90 -

Methyl 3-(3-N-BOC-Aminopropoxy)benzoate (11-2)

Following the procedure for coupling 1-1 to 1-2, 8-2 (2.8 g, 16.1 mmol) was coupled to 11-1 (Aldrich) (1.6 g, 10.7 mmol) to give 11-2 as a colorless oil after flash chromatography (silica, 15%

5 EtOAc/hexanes).

TLC R_f 0.28 (silica, 15% EtOAc/hexanes);

¹H NMR (400 MHz, CD₃OD) δ 7.62 (m, 1H), 7.56 (m, 1H), 7.40 (m, 1H), 7.19 (m, 1H), 4.09 (m, 2H), 3.93 (s, 3H), 3.27 (m, 2H), 1.99 (m, 2H), 1.47 (s, 9H).

10

3-(3-N-BOC-Aminopropoxy)benzoic acid (11-3)

A solution of 11-2 (3.3 g, 10.7 mmol), 1N NaOH (30 mL) and ethanol (50 mL) was heated at 60°C for 20 h. The cooled reaction mixture was acidified with 10% KHSO₄ and then extracted with EtOAc.

15 The organic portion was washed with brine, dried (MgSO₄) and concentrated to give 11-3 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 7.63 (m, 1H), 7.58 (m, 1H), 7.40 (m, 1H), 7.18 (m, 1H), 4.08 (m, 2H), 3.27 (m, 2H), 2.00 (m, 2H), 1.47 (s, 9H).

20

3-[3-(N-BOC-Aminopropoxy)]benzoyl-2(S)-phenylsulfonylamino-β-alanine tert-butyl ester (11-4)

Following the procedure for coupling 1-4 to 2-1, 11-3 (2.86 mg, 1.0 mmol) was coupled to 2-1 (296 mg, 1.0 mmol) to give

25 11-4 as a colorless oil after flash chromatography (silica, 50%

EtOAc/hexanes).

TLC R_f=0.27 (silica, 50% EtOAc/hexanes);

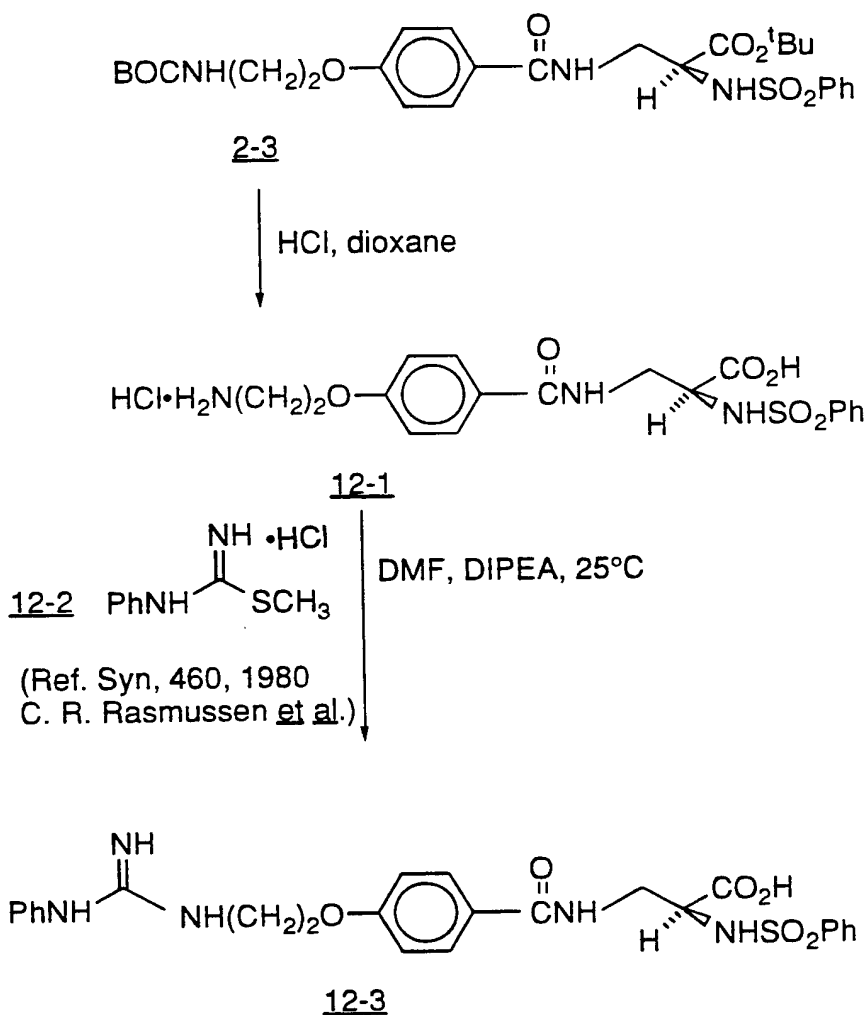
¹H NMR (300 MHz, CD₃OD) δ 7.67 (m, 2H), 7.32 (m, 3H), 7.13 (m, 3H), 6.91 (m, 1H), 4.03 (m, 1H), 3.95 (m, 2H), 3.55 (m, 1H), 3.39 (m, 30 1H), 3.12 (m, 2H), 1.88 (m, 2H), 1.32 (s, 9H), 1.16 (s, 9H).

- 91 -

3-[3-(Guanidino)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -
alanine (11-5)

Following the procedure for converting 10-4 to 10-5, 11-4
(350 mg, 0.64 mmol) was heated at 40°C for 3.0 h to give 11-5 as a
5 white solid after flash chromatography (silica, 10:1:1 ethanol/
NH₄OH/H₂O).
TLC R_f=0.28 (silica, 10:1:1 ethanol/NH₄OH/H₂O);
¹H NMR (400 MHz, CD₃OD) δ 7.77 (m, 2H), 7.60-7.25 (m, 6H), 7.18
(m, 1H), 4.28 (m, 1H), 4.18 (m, 2H), 3.73 (m, 1H), 3.56 (m, 1H), 3.47
10 (m, 2H), 2.13 (m, 2H).

- 92 -

SCHEME 12

4-(2-Aminoethyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine•HCl
(12-1)

A suspension of 2-3 (105 mg, 0.19 mmol) in 6N HCl (5 mL) was treated with dioxane (5 mL) to effect a homogeneous solution. After stirring for 20 h at ambient temperature, the solvents were evaporated and the resulting residue azeotroped with toluene to afford

10 12-1 as a colorless solid.

TLC R_f 0.48 (silica, 9:0.5:0.5 ethanol/H₂O/NH₄OH).

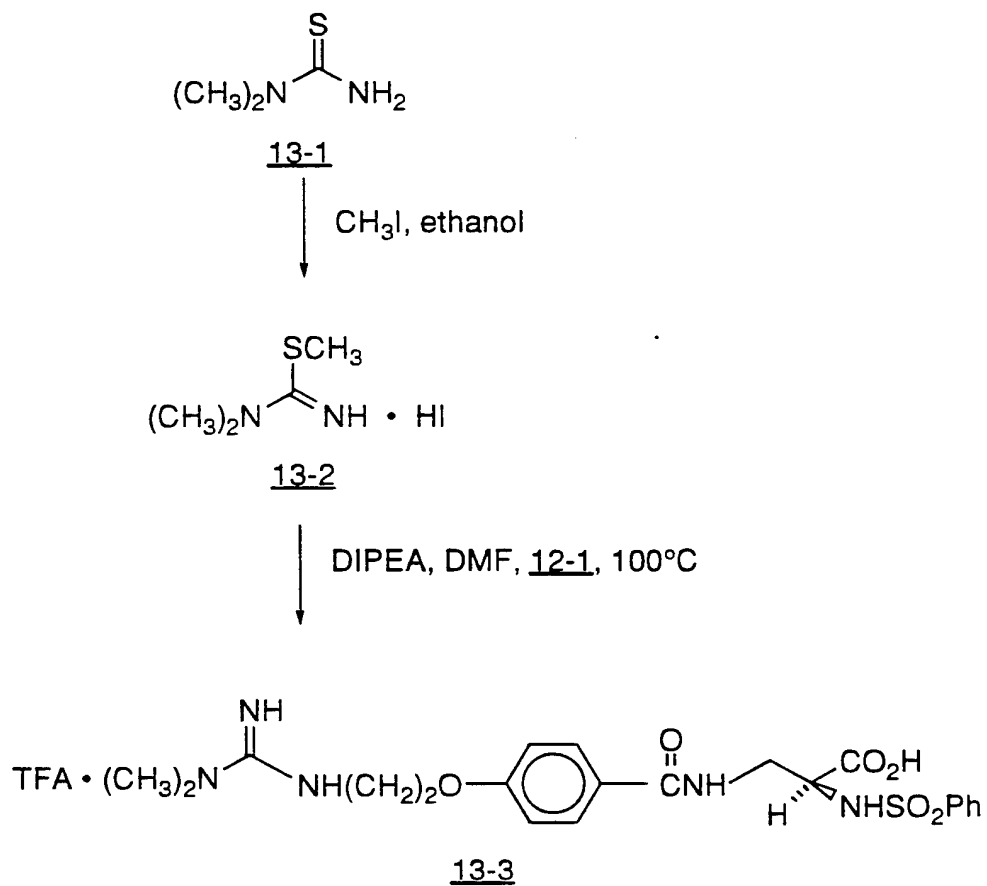
- 93 -

^1H NMR (300 MHz, CD_3OD) δ 7.82 (m, 2H), 7.78 (d, $J=9\text{H}$, 2H), 7.48 (m, 3H), 7.07 (d, $J=9\text{ Hz}$, 2H), 4.30 (m, 2H), 4.19 (m, 1H), 3.73 (m, 1H), 3.48 (m, 1H), 3.40 (m, 2H).

5 4-[2-(N-Phenylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-
 β -alanine (12-3)

A mixture of 12-1 (110 mg, 0.25 mmol), 12-2 (147 mg, 0.50 mmol), DIPEA (174 μL , 1.0 mmol) and DMF (5 mL) was stirred for 24 h at ambient temperature. Concentration and flash
10 chromatography (silica, 9.5:0.25:0.25 ethanol/ $\text{NH}_4\text{OH}/\text{H}_2\text{O}$) gave 12-3 as a colorless solid.
TLC R_f 0.50 (silica, 9.5:0.25:0.25 ethanol/ $\text{NH}_4\text{OH}/\text{H}_2\text{O}$);
 ^1H NMR (400 MHz, CD_3OD) δ 7.77 (m, 2H), 7.72 (d, $J=9\text{ Hz}$, 2H),
7.60-7.20 (m, 8H), 7.02 (d, $J=9\text{ Hz}$, 2H), 4.70 (m, 1H), 4.22 (m, 2H),
15 3.73 (m, 2H), 3.67 (m, 1H), 3.56 (m, 1H).

- 94 -

SCHEME 13

- 95 -

N,N-Dimethylthiomethyl amidine•HI (13-2)

The thiourea 13-1 (TransWorld) (5.0 g, 48 mmol) was suspended in ethanol (50 mL) at ambient temperature and treated with methyl iodide (4.5 mL, 72 mmol). After 2.0 h the reaction mixture was concentrated and the residue triturated with ether to give 13-2 as a pale yellow solid. mp=97-100°C.

¹H NMR (300 MHz, CD₃OD) δ 3.31 (s, 3H), 3.27 (s, 3H), 2.68 (s, 3H).

10 4-[2-(N,N-Dimethylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine•TFA salt (13-3)

A solution of 13-2 (246 mg, 1.0 mmol), 12-1 (222 mg, 0.5 mmol), DIPEA (261 μL, 1.5 mmol) and DMF (5 mL) was heated at 100°C for 18 h. The reaction mixture was then concentrated. Flash chromatography (silica, 9:0.5:0.5 to 9:1:1 ethanol/H₂O/NH₄OH) gave

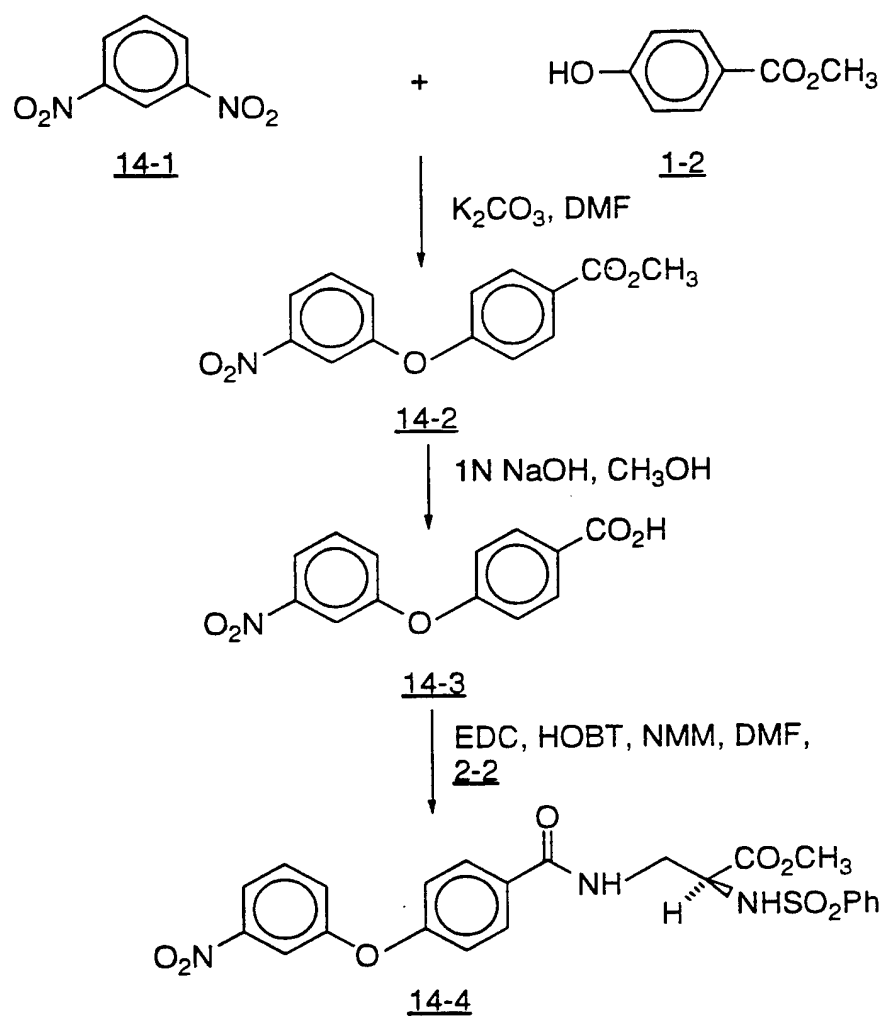
15 13-3 as a colorless solid after lyophilization.

TLC R_f 0.22 (silica, 9:1:1 ethanol/NH₄OH/H₂O);

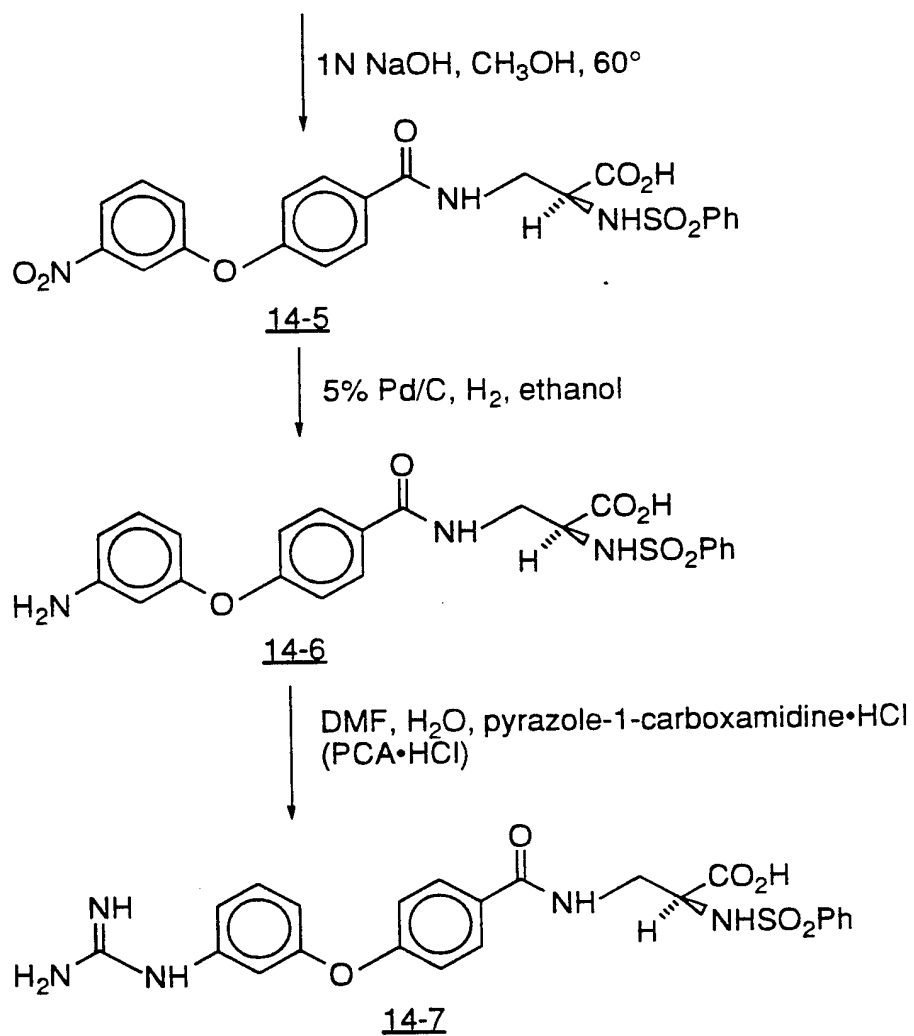
¹H NMR (300 MHz, CD₃OD) δ 7.88 (m, 2H), 7.80 (m, 2H), 7.52 (m, 3H), 7.00 (d, J=9 Hz, 2H), 4.20 (m, 2H), 3.80-3.50 (m, 4H), 3.30 (bs, 6H), 3.03 (s, 3H).

20

- 96 -

SCHEME 14

- 97 -

SCHEME 14 (CONT'D)

- 98 -

Methyl 4-(nitrophen-3-yloxy)benzoate (14-2)

A mixture of 14-1 (Aldrich) (1.6 g, 10 mmol), 1-2 (1.5 g, 10 mmol), K₂CO₃ (1.4 g, 10 mmol) and DMF (20 mL) was refluxed for 7.0 h. After cooling most of the DMF was removed *in vacuo*. The dark residue was diluted with ether and then washed with H₂O and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 20% ether/hexanes) gave 14-2 as a yellow solid.

TLC R_f 0.16 (silica, 20% ether/hexanes);

¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, J=9 Hz, 2H), 8.03 (m, 1H), 7.87 (m, 1H), 7.55 (m, 1H), 7.40 (m, 1H), 7.06 (d, J= 9 Hz, 2H), 3.93 (s, 3H).

4-(Nitrophen-3-yloxy)benzoic acid (14-3)

A solution of 14-2 (160 mg, 0.58 mmol), 1N NaOH (5.8 mL) and CH₃OH (10 mL) was stirred at ambient temperature for 24 h. The reaction mixture was concentrated and the residue dissolved in H₂O and washed with ether. The aqueous portion was then acidified with NaHSO₄ and extracted with EtOAc (2x). The combined EtOAc portions were dried (MgSO₄) and then concentrated to give 14-3 as a pale yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 8.18 (d, J=9 Hz, 2H), 8.07 (m, 1H), 7.91 (m, 1H), 7.58 (m, 1H), 7.42 (m, 1H), 7.10 (d, J=9 Hz, 2H).

4-(Nitrophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine methyl ester (14-4)

A solution of 14-3 (340 mg, 1.3 mmol), 2-2 (386 mg, 1.3 mmol), HOBt (271 mg, 1.8 mmol), and DMF (6 mL) at -15°C was treated with EDC (339 mg, 1.8 mmol). The pH of the solution was adjusted to about 8.0 with NMM followed by removal of the cooling bath. After 20 h the reaction mixture was concentrated and the residue dissolved in EtOAc. The EtOAc solution was washed with H₂O, sat. NaHCO₃ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 5% to 10% acetone/CH₂Cl₂) gave 14-4 as a colorless foam.

- 99 -

TLC R_f 0.14 (silica, 5% acetone/CH₂Cl₂);

¹H NMR (300 MHz, CDCl₃) δ 8.01 (m, 1H), 7.85 (m, 5H), 7.53 (m, 4H), 7.36 (m, 1H), 7.08 (d, J=9 Hz, 2H), 6.80 (m, 1H), 5.80 (m, 1H), 4.10 (m, 1H), 3.93 (m, 1H), 3.69 (m, 1H), 3.67 (s, 3H).

5

4-(Nitrophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine
(14-5)

Following the procedure for converting 14-2 to 14-3, 14-4 (608 mg, 1.2 mmol) was saponified at 60°C to give 14-5 as a pale yellow solid.

10

¹H NMR (300 MHz, CD₃OD) δ 8.05 (m, 1H), 7.85 (m, 5H), 7.65 (m, 1H), 7.48 (m, 4H), 7.12 (d, J=9 Hz, 2H), 4.21 (m, 1H), 3.75 (m, 1H), 3.52 (m, 1H).

15 4-(Aminophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine
(14-6)

A mixture of 14-5 (560 mg, 1.2 mmol), 5% Pd/C (110 mg), and ethanol (50 mL) was stirred under a hydrogen atmosphere (1 atm) at ambient temperature for 8 h. Some precipitate had formed so the mixture was heated to dissolve the solid and then filtered hot through a celite pad to remove the catalyst. Concentration of the filtrate gave 14-6 as a colorless solid.

20

TLC R_f 0.85 (silica, 9:0.5:0.5 ethanol/NH₄OH/H₂O);

¹H NMR (300 MHz, CD₃OD) δ 7.83 (d, J=7 Hz, 2H), 7.72 (d, J=9 Hz, 2H), 7.46 (m, 3H), 7.10 (m, 1H), 6.98 (d, J=9 Hz, 2H), 6.55 (m, 1H), 6.42 (m, 1H), 6.35 (m, 1H), 4.17 (m, 1H), 3.72 (m, 1H), 3.50 (m, 1H).

25

- 100 -

4-(Guanidinophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine
(14-7)

A solution of 14-6 (45 mg, 0.10 mmol), PCA•HCl (14 mg, 0.1 mmol) and DMF/H₂O (1:1; 1 mL) was heated at 120°C for 20 h.

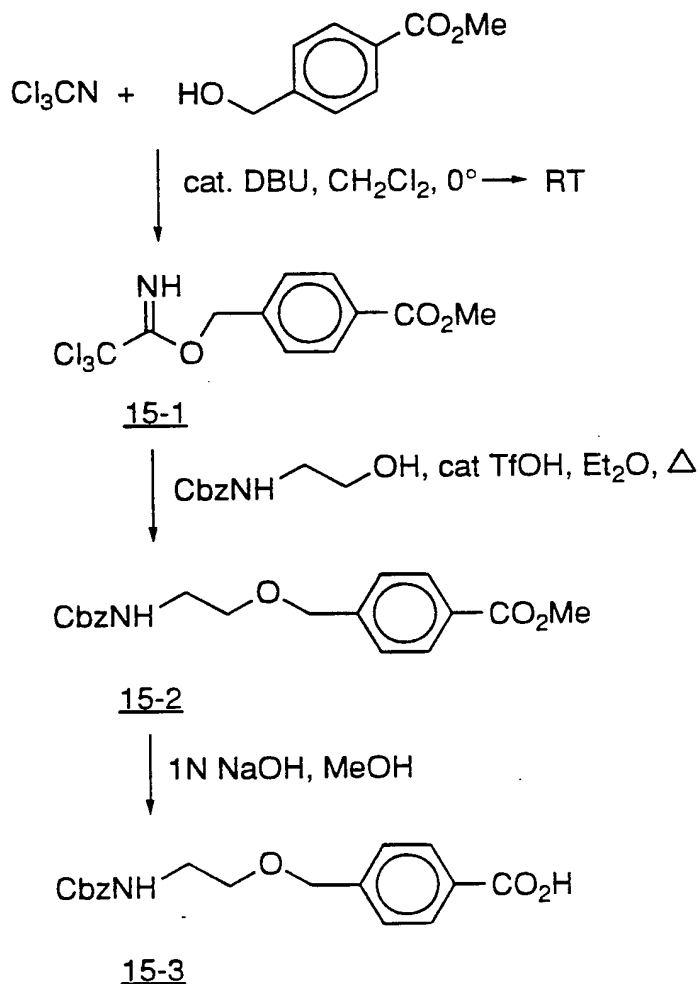
- 5 Concentration and flash chromatography (silica, 9:0.5:0.5 ethanol/
 NH₄OH/H₂O) gave 14-7 as a colorless solid.

TLC R_f 0.20 (silica, 9:0.5:0.5 ethanol/NH₄OH/H₂O);

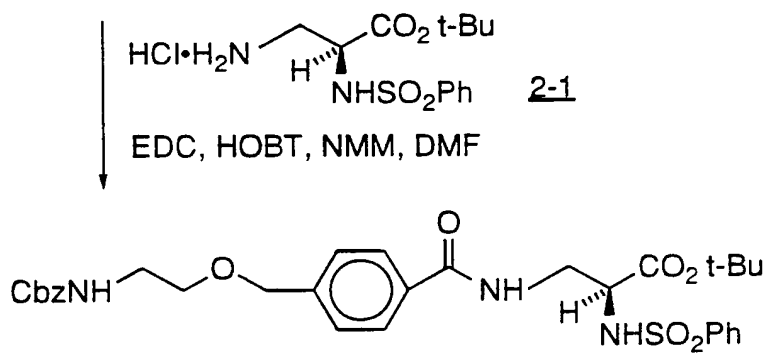
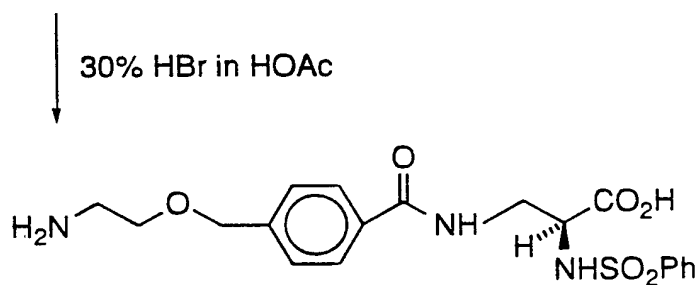
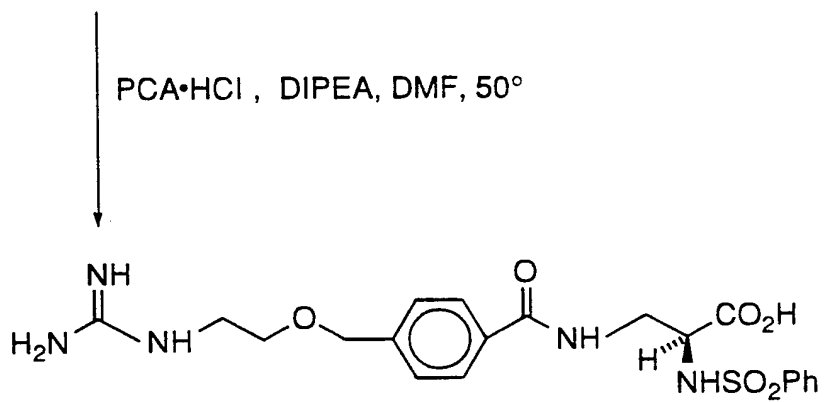
¹H NMR (300 MHz, CD₃OD/40% NaOD/D₂O) δ 7.80 (m, 4H), 7.31
 (m, 4H), 7.00 (d, J=9 Hz, 2H), 6.79 (m, 1H), 6.68 (m, 1H), 6.60 (m,

10 1H), 3.67 (m, 2H), 3.35 (m, 1H).

SCHEME 15



- 101 -

SCHEME 15 (CONT'D)15-315-415-515-6

- 102 -

Methyl 4-(trichloromethyliminooxymethyl)benzoate (15-1)

Methyl 4-hydroxymethylbenzoate (Aldrich), (1.22 g, 7.35 mmol), trichloroacetonitrile (0.81 mL, 8.1 mmol), and DBU (0.11 mL, 0.74 mmol) were combined in CH₂Cl₂ at 0°. After warming to RT for

5 3 h the reaction mixture was concentrated and purified by flash chromatography (silica, 40% EtOAc/hex) providing 15-1.

R_f 0.77 (silica, 50% EtOAc/hexane);

¹H NMR (300 MHz, CDCl₃) δ 8.42 (s, 1H), 8.06 (d, J=8 Hz, 2H), 7.50 (d, J=9 Hz, 2H), 5.40 (s, 2H), 3.92 (s, 3H).

10

Methyl 4-[2-(N-Cbz-amino)ethyloxymethyl]benzoate (15-2)

Imidate 15-1 (1.5 g, 4.8 mmol) and N-Cbz-aminoethanol (1.0 g, 5.1 mmol) were combined with Et₂O (50 ml), then TfOH (100 μL, 1.1 mmol) was added (exothermic). The reaction mixture was

15 stirred at RT for 24 h, then heated at reflux for 16 h before diluting with EtOAc, washing with water, 10% KHSO₄, 1N NaOH, and brine, drying (MgSO₄) and concentration. Flash chromatography (silica, 20% then 40% EtOAc/hexane) provided 15-2 as a clear oil.

R_f 0.53 (silica, 50% EtOAc/hexane).

20 ¹H NMR (300 MHz, CDCl₃) δ 8.0 (d, J=8 Hz, 2H), 7.50-7.30 (m, 7H), 5.18 (br m, 1H), 5.10 (s, 2H), 4.56 (s, 2H), 3.92 (s, 3H), 3.58 (br m, 2H), 3.45 (br m, 2H).

4-[2-(N-Cbz-amino)ethoxymethyl]benzoic acid (15-3)

25 Ester 15-2 (500 mg, 1.46 mmol) and 1N NaOH (3.6 mL, 3.6 mmol) were combined in 14 mL MeOH. After 3 h the mixture was concentrated, diluted with EtOAc, and extracted with H₂O. The aqueous layer was acidified with 10% KHSO₄ and extracted with EtOAc, and this organic layer was washed with brine, dried (MgSO₄),

30 and concentrated, providing 15-3 as a white solid.

R_f 0.62 (silica, 19:1:1 CH₂Cl₂/MeOH/HOAc).

¹H NMR (300 MHz, CD₃OD) δ 8.0 (d, J=8 Hz, 2H), 7.5-7.3 (m, 7H), 5.07 (s, 2H), 4.59 (s, 2H), 3.56 (t, J=5 Hz, 2H), 3.34 (t, J=5 Hz, 2H).

- 103 -

4-[2-(N-Cbz-Amino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino-
 β -alanine t-butyl ester (15-4)

Acid 15-3 (300 mg, 0.91 mmol), amine 2-1 (325 mg, 0.91 mmol), EDC (209 mg, 1.09 mmol), HOBT (148 mg, 1.10 mmol), and
5 NMM (300 μ L, 2.7 mmol) were combined in 4.5 mL DMF. After 16 h the mixture was diluted with EtOAc, washed with water, 10% KHSO₄, sat NaHCO₃, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 70% EtOAc/hexane) provided 15-4 as an off-white solid.

10 R_f 0.77 (silica, EtOAc).

¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J=7 Hz, 2H), 7.72 (d, J=8 Hz, 2H), 7.40-7.20 (m, 10H), 7.0 (br s, 1H), 5.26 (br m, 1H), 5.09 (s, 2H), 4.49 (s, 2H), 3.80-3.70 (m, 2H), 3.5-3.45 (m, 3H), 3.41 (m, 2H), 1.24 (s, 9H).

15

4-(2-Aminoethyloxymethyl)benzoyl-2(S)-phenylsulfonylamino- β -
alanine (15-5)

Cbz-ester 15-4 (200 mg, 0.33 mmol) was treated with 4 mL 30% HBr in HOAc for 2 h then concentrated and purified by flash
20 chromatography (silica, 50:1:1 EtOH/NH₄OH/H₂O) providing 15-5 as a white solid.

R_f 0.42 (silica, 20:1:1 EtOH/NH₄OH/H₂O).

¹H NMR (400 MHz, D₂O) δ 7.66 (d, J=9 Hz, 2H) 7.52 (d, J=8 Hz, 2H), 7.38 (d, J=8 Hz, 2H), 7.33-7.25 (m, 3H), 7.58 (s, 2H), 3.80 (dd, J=10, 4
25 Hz, 1H), 3.66 (br t, J=5 Hz, 2H), 3.58 (dd, J=14, 4 Hz, 1H), 3.31 (dd, J=14, 10 Hz, 1H), 3.07 (br m, 2H).

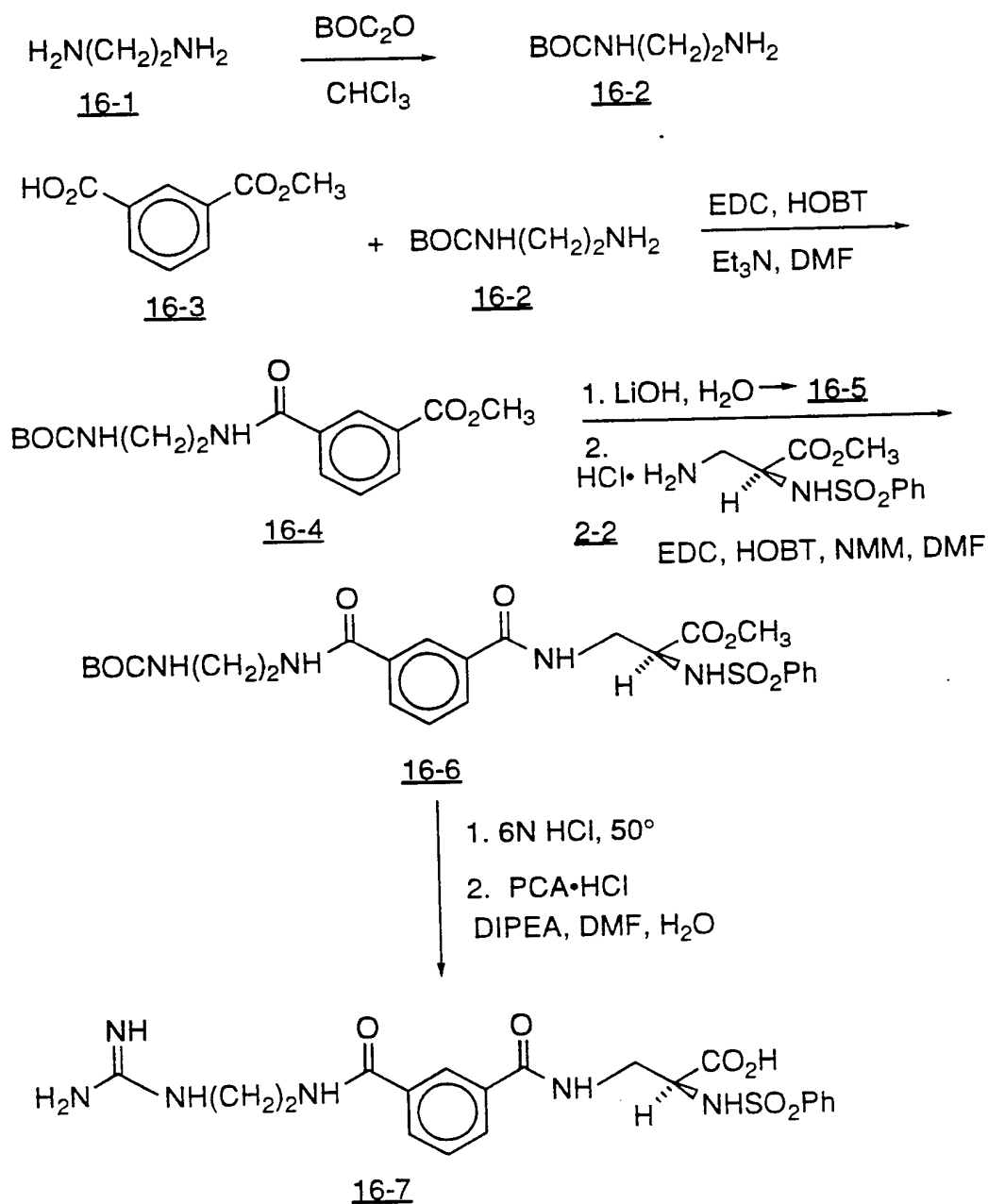
4-[2-(Guanidino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino- β -
alanine (15-6)

30 Amine 15-5 (40 mg, 0.095 mmol), PCA•HCl (15 mg, 0.10 mmol), and DIPEA (35 mL, 0.20 mmol) were combined in 1 mL DMF and heated at 50° for 16 h. Concentration, and flash chromatography (silica, 20:1:1 EtOH/NH₄OH/H₂O) provided 15-6 as a white solid.
R_f 0.19 (silica, 20:1:1 EtOH/NH₄OH/H₂O).

- 104 -

^1H NMR (400 MHz, D_2O) δ 7.61 (d, $J=8$ Hz, 2H), 7.46 (d, $J=7$ Hz, 2H), 7.31 (d, $J=8$ Hz, 2H), 7.28-7.18 (m, 3H), 4.51 (s, 2H), 3.75 (m, 1H), 3.56 (m, 2H), 3.54-3.44 (m, 2H), 3.25 (m, 2H).

5

SCHEME 16

- 105 -

2-(N-BOC-Amino)ethylamine (16-2)

Ethylenediamine (16-1) (Aldrich) (18.04 g, 0.50 mol) in CHCl₃ (200 ml) was treated with a solution of BOC₂O (13.1 g, 0.06 moles) in CHCl₃ (100 ml) at room temperature over 1 h. This was
5 stirred for 16 h, filtered, and concentrated to give 16-2 as a clear oil.

Methyl 3-[2-(N-BOC-amino)ethylaminocarbonyl]benzoate (16-4)

A solution of methyl 3-carboxybenzoate (16-3) (Aldrich) (0.9 g, 5 mmol), 16-2 (0.8 g, 5 mmol), and HOBT (0.74 g, 5.5 mmol)
10 in DMF (20 ml) was treated with Et₃N (1.0 g, 10 mmol) followed by EDC (1.15 g, 6.0 mmol). After stirring for 16 h the solvent was removed, the residue was taken up in H₂O (100 mL), and extracted with 3x75 ml portions of EtOAc. The organic extract was washed
15 consecutively with 10% KHSO₄, brine, satd. NaHCO₃, brine, and dried (Na₂SO₄). Solvent removal gave a residue that was purified by flash chromatography (silica, 95% hexanes/EtOAc) to give crude 16-4. This was further purified by chromatography (silica, 70%/acetone/hexanes) to give pure 16-4.

R_f 0.3 (silica, 70% hexanes/acetone).

20 ¹H NMR (300 MHz, CDCl₃) δ 8.46 (s, 1H), 8.13-8.20 (dd, 1H), 8.03-8.10 (dd, 1H), 7.48-7.57 (t, 1H), 7.30-7.45 (m, 1H), 4.95-5.08 (m, 1H), 3.95 (s, 3H), 3.52-3.62 (m, 2H), 3.38-3.48 (m, 2H), 1.42 (s, 9H).

25 3-[2-(N-BOC-Amino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine methyl ester (16-6)

16-4 (0.98 g, 3.03 mmoles) was dissolved in THF(1)/MeOH(1)/H₂O(1) (30 ml) and treated with LiOH (0.38 g, 9.1 mmoles). After 10 h, the solvent was removed, the residue acidified to pH 2-3 with 10% KHSO₄ solution, and extracted with EtOAc. The organic
30 extract was dried (Na₂SO₄), concentrated, and the residue was purified by flash chromatography (silica, 95% hexanes/EtOAc) to give the desired acid 16-5.

This acid (0.46 g, 1.5 mmoles) was dissolved in DMF (20 ml) and treated with 2-2 (0.44 g, 1.5 mmoles), HOBT (0.22 g, 1.65

- 106 -

mmoles), NMM (0.45 g, 4.5 moles) followed by EDC (0.34 g, 1.8 mmoles). After stirring at room temperature for 16 h, the solvent was removed and the residue was taken up in H₂O (75 ml), and extracted with EtOAc. The organic extract was washed with 10% KHSO₄, brine,
5 dried (Na₂SO₄) and concentrated to give 16-6 as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 8.17 (s, H), 7.78-7.97 (dd, 4H), 7.20-7.65 (m, 6H), 6.40-6.65 (b, 1H), 5.00-5.55 (b, 1H), 4.13-4.24 (m, 1H), 3.68-3.88 (m, 2H), 3.55 (s, 3H), 3.45-3.60 (bt, 2H), 3.30-3.44 (bt, 2H), 1.42 (s, 9H).

10

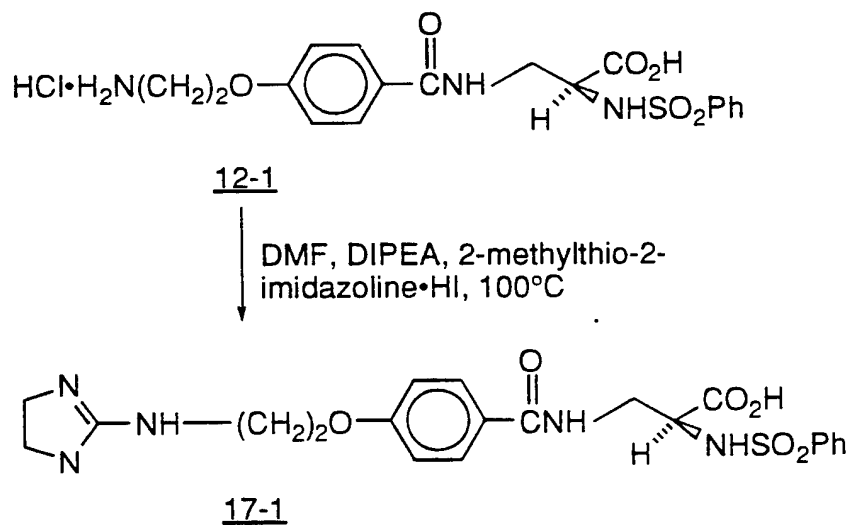
3-[2-(Guanidino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine (16-7)

A suspension of 16-6 in 6N HCl was stirred at room temperature while the ester gradually dissolved over 1 h. After 24 h
15 the reaction was heated at 50° for 5 h, cooled and filtered. This solid was triturated with EtOAc and filtered to provide the desired acid.

This acid was treated with PCA•HCl as described for 1-8 to provide crude product. This was purified by flash chromatography on silica gel eluting with EtOH(10)/NH₄OH(0.5)/H₂O(0.5) to give 16-7.

20 ¹H NMR (300 MHz, CD₃OD) δ 8.24 (s, 1H), 7.77-8.03 (m, 4H), 7.36-7.60 (m, 4H), 3.78-3.87 (dd, 1H), 3.50-3.72 (m, 4H), 3.32-3.47 (t, 2H).

- 107 -

SCHEME 17

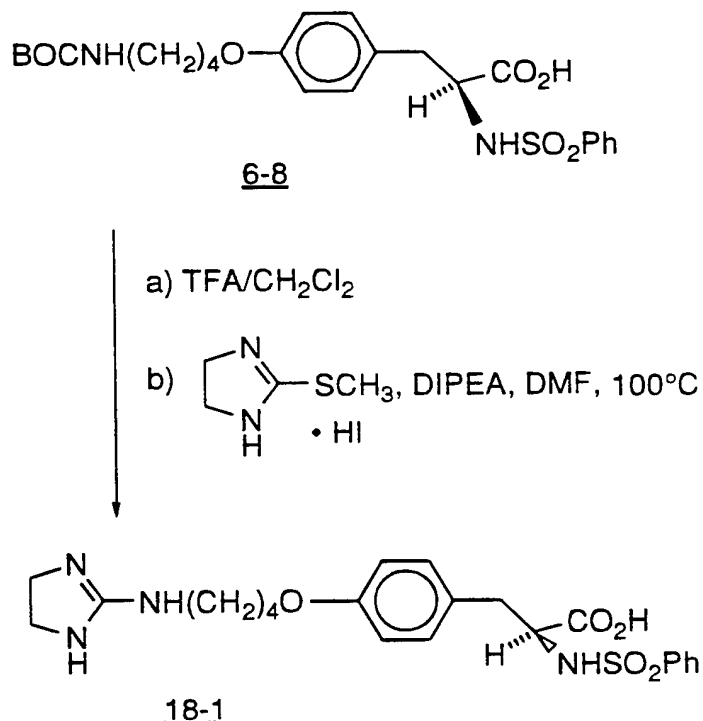
5 4-[2-(N-(2-Imidazolin-2-yl)amino)ethyloxy]benzoyl-2(S)-phenyl-
sulfonylamino-β-alanine (17-1)

A solution of 12-1 (89 mg, 0.2 mmol), 2-methylthio-2-imidazoline·HI (98 mg, 0.4 mmol), DIPEA (139 μL, 0.8 mmol) and DMF was stirred at 100°C for 20 h. Concentration of the cooled reaction mixture followed by chromatography (silica, 9:0.5:0.5 ethanol/NH₄OH/H₂O) gave 17-1 as a colorless lyophilizate.

10 TLC R_f 0.21 (silica, 9:0.5:0.5 ethanol/NH₄OH/H₂O);
¹H NMR (400 MHz, CD₃OD) δ 7.87 (m, 2H), 7.80 (d, J=9Hz, 2H), 7.50 (m, 3H), 6.98 (d, J=9 Hz, 2H), 4.17 (m, 2H), 3.80-3.50 (m, 5H), 3.73 (bs, 4H).

15

- 108 -

SCHEME 18

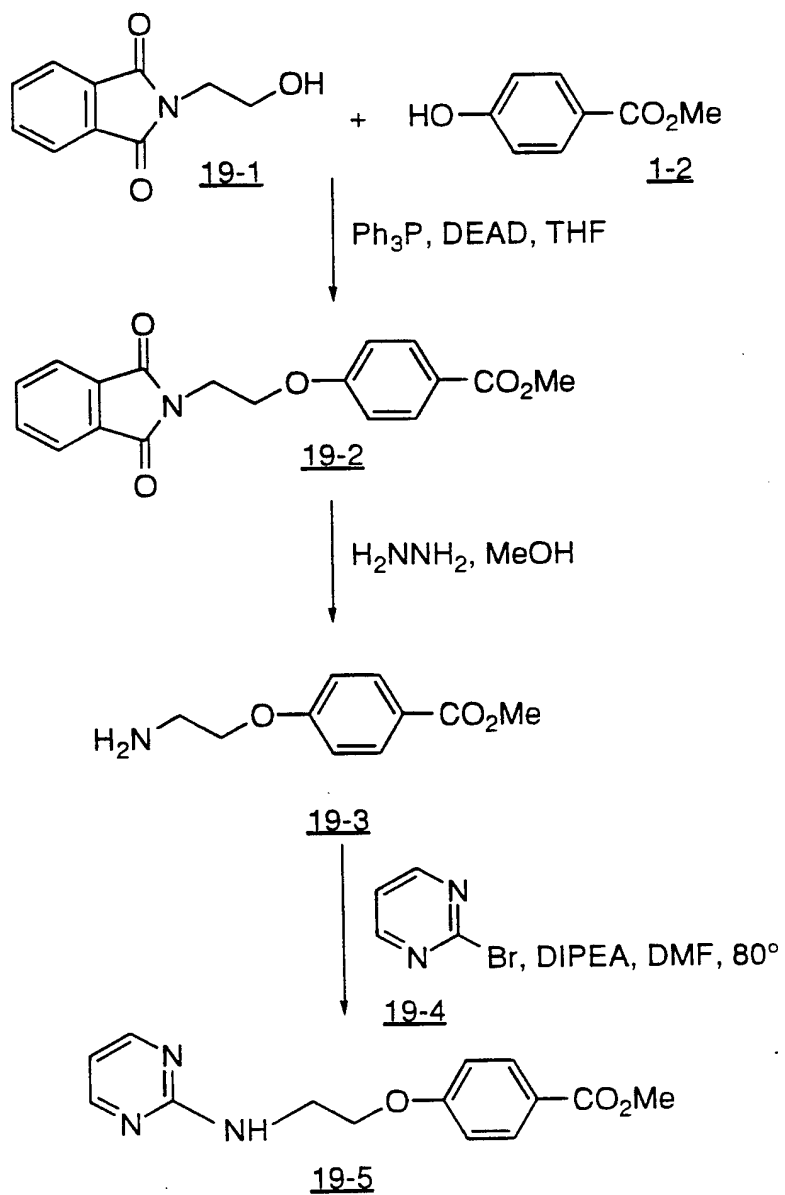
5 2(S)-Phenylsulfonylamino-3-[(4-(N-(imidazolin-2-yl)aminobutyloxy)-phenyl]propionic acid (18-1)

A solution of 6-8 (200 mg, 0.41 mmol), TFA (2 mL), and CH₂Cl₂ (2 mL) was stirred at ambient temperature for 1.0 h. The solution was concentrated and the residual TFA removed azeotropically
 10 with toluene. The resulting oil was dissolved in DMF (2 mL) and then treated with DIPEA (211 µL, 1.6 mmol) and 2-methylthio-2-imidazoline • HI (198 mg, 0.82 mmol). The resulting solution was heated at 100°C for 20h. Concentration of the cooled reaction mixture followed by flash chromatography (silica, 10:0.2:0.2→10:1:1
 15 ethanol/NH₄OH/H₂O) gave 18-1 as a white solid.
 TLC R_f 0.38 (silica, 10:1:1 ethanol/NH₄OH/H₂O).

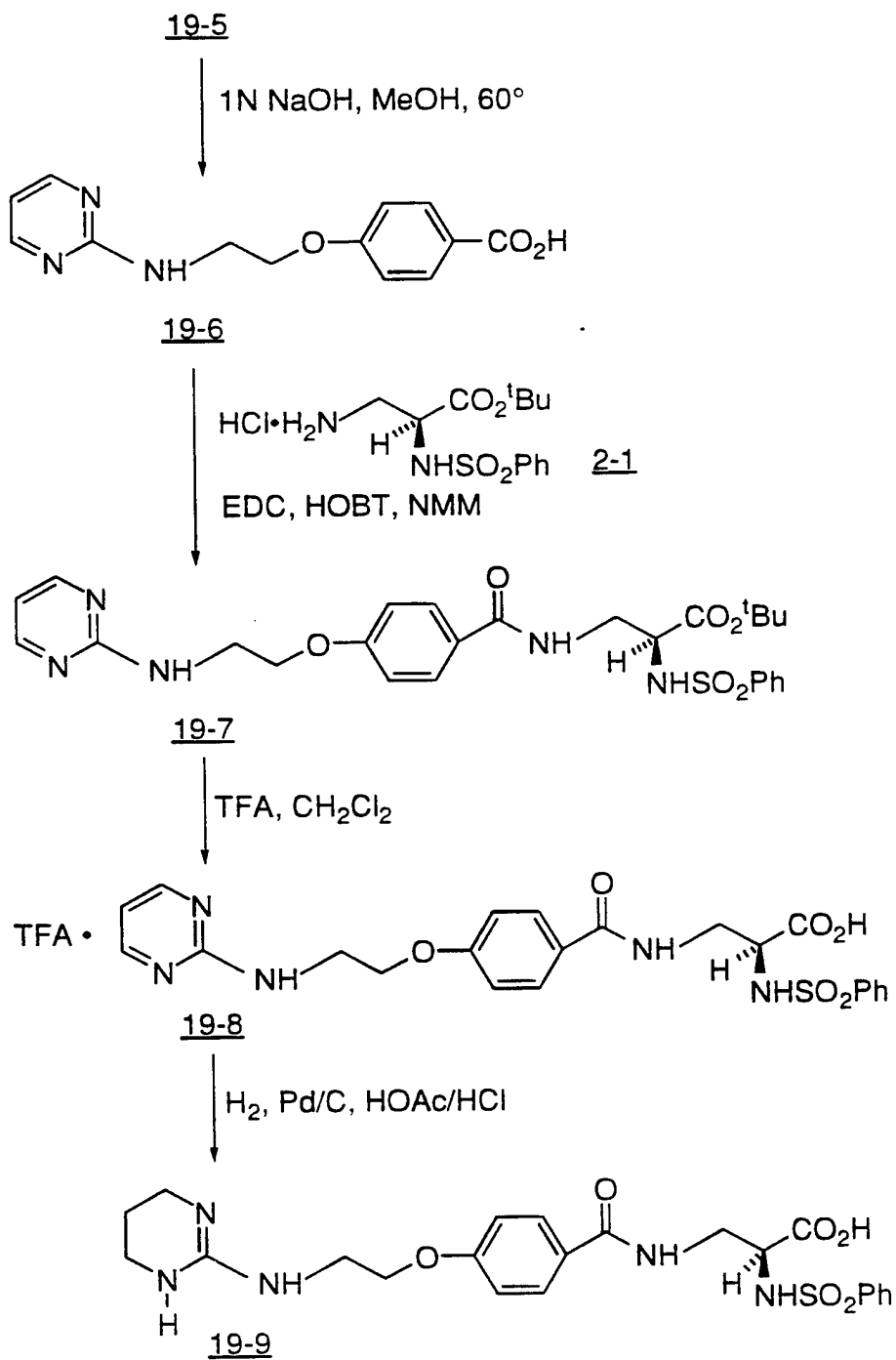
- 109 -

^1H NMR (400 MHz, D_2O) δ 7.45-7.20 (m, 5H), 6.83 (d, $J=9$ Hz, 2H), 6.56 (d, $J=9$ Hz, 2H), 3.87 (m, 3H), 3.48 (m, 4H), 3.09 (m, 2H), 2.90 (m, 1H), 3.57 (m, 1H), 1.60 (m, 4H).

5

SCHEME 19

- 110 -

SCHEME 19 (CONT'D)

- 111 -

Methyl 4-(2-Phthalimidoethoxy)benzoate (19-2)

A solution of N-(2-hydroxyethyl)phthalimide (Aldrich, 19-1, 6.36 g, 33 mmol) and DEAD (5.7 mL, 36 mmol) in 25 mL THF and 10 mL DMF was added to a solution of methyl 4-hydroxybenzoate (1-2, 5.00 g, 33 mmol) and Ph₃P (9.53 g, 36 mmol) in 100 mL THF during 1 h. After an additional hour the reaction was diluted with ether, washed twice with water, then 1N NaOH and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica gel, CH₂Cl₂) provided 19-2 as a white solid.

R_f 0.18 (silica, CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, J=9Hz, 2H), 7.87 (m, 2H), 7.74 (m, 2H), 6.84 (d, J=9Hz, 2H), 4.28 (t, J=6Hz, 2H), 4.14 (t, J=6Hz, 2H), 3.87 (s, 3H).

Methyl 4-(2-Aminoethoxy)benzoate (19-3)

19-2 (1.59 g, 4.89 mmol) was suspended in 25 mL MeOH. Upon addition of hydrazine (2.0 mL, 64 mmol) the reaction became homogeneous. After 20 h a heavy precipitate had formed. The pH was adjusted to 1 by addition of 6N HCl, MeOH evaporated, and the solid suspended in 1N HCl. After filtering through Celite, the filtrate was washed with CH₂Cl₂, the pH was adjusted to 12 with 6N NaOH. The aqueous layer was extracted with fresh CH₂Cl₂. This organic phase was dried (Na₂SO₄) and concentrated providing 19-3 as a white solid.

R_f 0.22 (silica, 9:1:1 CH₂Cl₂/MeOH/HOAc).

¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, J=9Hz, 2H), 6.93 (d, J=9Hz, 2H), 4.04 (t, J=5Hz, 2H), 3.89 (s, 3H), 3.11 (t, J=5Hz, 3H), 1.35 (br s, 2H).

- 112 -

Methyl 4-[2-(Pyrimidin-2-yl)amino]ethyloxy]benzoate (19-5)

Amine 19-3 (4.30 g, 22 mmol), 19-4 (3.51 g, 22 mmol) and DIPEA (3.8 mL, 22 mmol) were heated in 50 mL DMF at 80° for 16 h. The cooled mixture was concentrated, then diluted with EtOAc, washed with 1N NaOH and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% acetone/CH₂Cl₂) provided white crystalline 19-5.

R_f 0.42 (silica, 10% acetone/CH₂Cl₂).

¹H NMR (300 MHz, CDCl₃) δ 8.29 (d, J=5Hz, 2H), 7.99 (d, J=9Hz, 2H), 6.93 (d, J=9Hz, 2H), 6.57 (t, J=5Hz, 1H), 5.53 (br m, 1H), 4.20 (t, J=5Hz, 2H), 3.88 (s, 3H) 3.88 (overlapped t, 2H).

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoic acid (19-6)

Pyrimidine ester 19-5 (3.31 g, 12.1 mmol) was combined with 1N NaOH (30 mL, 30 mmol) in 50 mL EtOH. After 2 h at 60° the mixture was cooled and 30 mL 1N HCl was added (final pH 5). The resulting white precipitate was collected on a frit, washed with water, and dried providing 19-6.

R_f 0.67 (silica, 10:1:1 EtOH/NH₄OH/H₂O).

¹H NMR (300 MHz, DMSO) δ 9.02 (d, J=5Hz, 2H), 8.60 (d, J=9Hz, 2H), 8.05 (t, J=6Hz, 1H), 7.76 (d, J=9Hz, 2H), 7.32 (t, J=5Hz, 1H), 4.89 (t, J=6Hz, 2H), 4.38 (q, J=6Hz, 2H), 4.06 (s, 1H).

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine tert-butyl ester (19-7)

Acid 19-6 (0.770 g, 2.97 mmol), amine 2-1 (1.0 g, 2.97 mmol), NMM (1.14 μL, 10.4 mmol) and HOBt (0.522 g, 3.86 mmol) were combined in 30 mL DMF, cooled to 0°, and EDC (0.740 g, 3.86 mmol) was added. The mixture was stirred at RT for 3 days, diluted with ethyl acetate, washed twice with water, sat. NaHCO₃, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 80% EtOAc/hexanes) provided 19-7 as a waxy solid. R_f 0.23 (silica, 80% EtOAc/hexane).

- 113 -

¹H NMR (300 MHz, CDCl₃) δ 8.31 (d, J=5 Hz, 2H), 7.85 (d, J=7 Hz, 2H), 7.73 (d, J=9 Hz, 2H), 7.60-7.45 (m, 3H), 6.90 (d, J=9 Hz, 2H), 6.67 (br m, 1H), 6.57 (t, J=5 Hz, 1H), 5.94 (d, J=8 Hz, 1H), 5.68 (br m, 1H), 4.17 (t, J=5 Hz, 2H), 4.00-3.83 (m, 4H), 3.59 (m, 1H), 1.28 (s, 9H).

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine trifluoroacetate (19-8)

Ester 19-7 (1.05 g, 1.86 mmol) and anisole (0.40 mL, 3.7 mmol) were dissolved in CH₂Cl₂ (9 mL), cooled to 0°, and TFA (9 mL) was added. After 2 h at 0° and 16 h at 20°, the reaction was concentrated, azeotroped with toluene, and triturated with Et₂O providing 19-8 as a white solid.

R_f 0.30 (silica, 22:20:1:1 EtOAc/EtOH/NH₄OH/H₂O).

¹H NMR (400 MHz, CD₃OD) 8.45 (br, 2H), 7.82 (dt, J=7, 2 Hz, 2H), 7.72 (d, J=9 Hz, 2H), 7.50 (tm, J=7 Hz, 1H), 7.42 (tm, J=8 Hz, 2H), 6.99 (d, J=9 Hz, 2H), 6.82 (t, J=5 Hz, 1H), 4.25 (t, J=5 Hz, 2H), 4.18 (dd, J=9, 5 Hz, 1H), 3.88 (t, J=5 Hz, 2H), 3.71 (dd, J=14, 5 Hz, 1H), 3.48 (m, 1H).

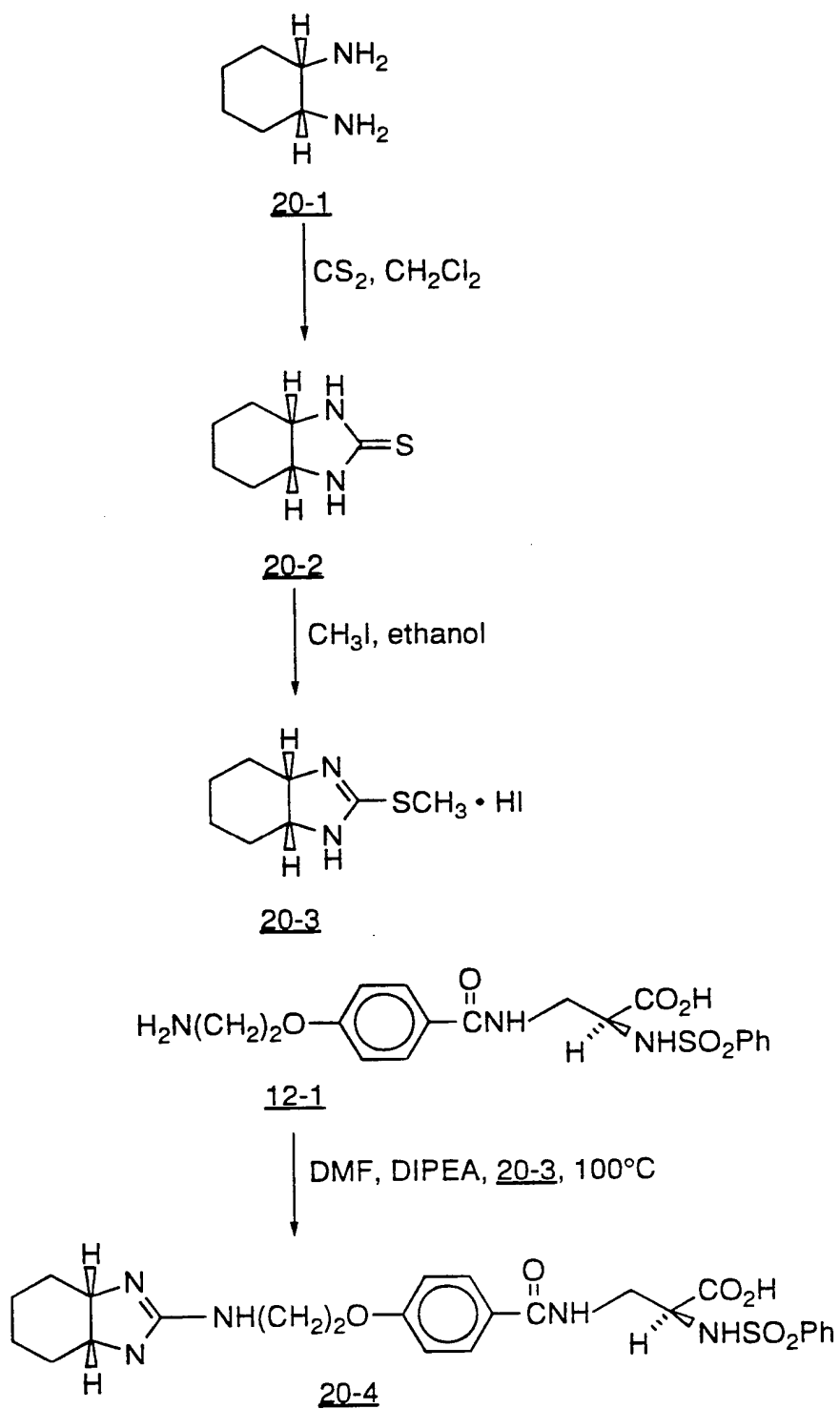
4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (19-9)

Pyrimidine 19-8 (1.05 g, 1.75 mmol) was dissolved in a mixture of acetic acid (50 mL) and conc HCl (4.5 mL). After addition of 10% Pd/C (450 mg) the mixture was shaken on a Parr hydrogenator under 45 psi H₂ pressure for 2 h. The reaction mixture was filtered, concentrated, azeotroped with toluene, and purified by flash chromatography (silica 20:1:1 then 8:1:1 EtOH/NH₄OH/H₂O) providing 19-9 as a white solid.

R_f 0.35 (8:1:1, EtOH/NH₄OH/H₂O).

¹H NMR (300 MHz, CD₃OD + DCl) δ 7.84 (d m, J=7 Hz, 2H), 7.74 (d, J=9 Hz, 2H), 7.50-7.40 (m, 3H), 7.02 (d, J=9 Hz, 2H), 4.22-4.17 (m, 3H), 3.72 (dd, J=14, 5 Hz, 1H), 3.60 (t, J=5 Hz, 2H), 3.49 (dd, J=14, 9 Hz, 1H), 3.38 (t, J=5 Hz, 4H), 1.95 (qn, J=6 Hz, 2H).

- 114 -

SCHEME 20

- 115 -

Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-thione (20-2)

- A solution of carbon disulfide (1.1 mL, 17.9 mmol) and CH₂Cl₂ (10 mL) was treated dropwise with cis-1,2-diaminocyclohexane 20-1 (Aldrich) (2.0 g, 17.5 mmol) while maintaining the reaction mixture temperature below 20°C with an ice bath. The reaction mixture was stirred at ambient temperature for 2.0 h after the addition was complete. Concentration followed by refluxing the resulting solid in H₂O (20 mL) for 20 h gave a yellow solution. The cooled solution was extracted with CH₂Cl₂ and the CH₂Cl₂ portion was dried (MgSO₄) and concentrated. The pale yellow solid was recrystallized from CH₂Cl₂/ether to give 20-2 as a pale yellow solid. mp = 164-166°C. ¹H NMR (300 MHz, CDCl₃) δ 6.30 (bs, 2H), 3.90 (m, 2H), 1.80-1.30 (m, 8H).

15 2-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]methylsulfide (20-3)

- A suspension of 20-2 (1.3 g, 8.3 mmol) in ethanol (5 mL) at ambient temperature was treated with iodomethane (0.8 mL, 12.5 mmol). After 20 h the ethanol was evaporated and the resulting solid triturated with acetone to give 20-3 as a solid. ¹H NMR (300 MHz, CD₃OD) δ 4.22 (m, 2H), 2.67 (s, 3H), 2.00-1.40 (m, 8H).

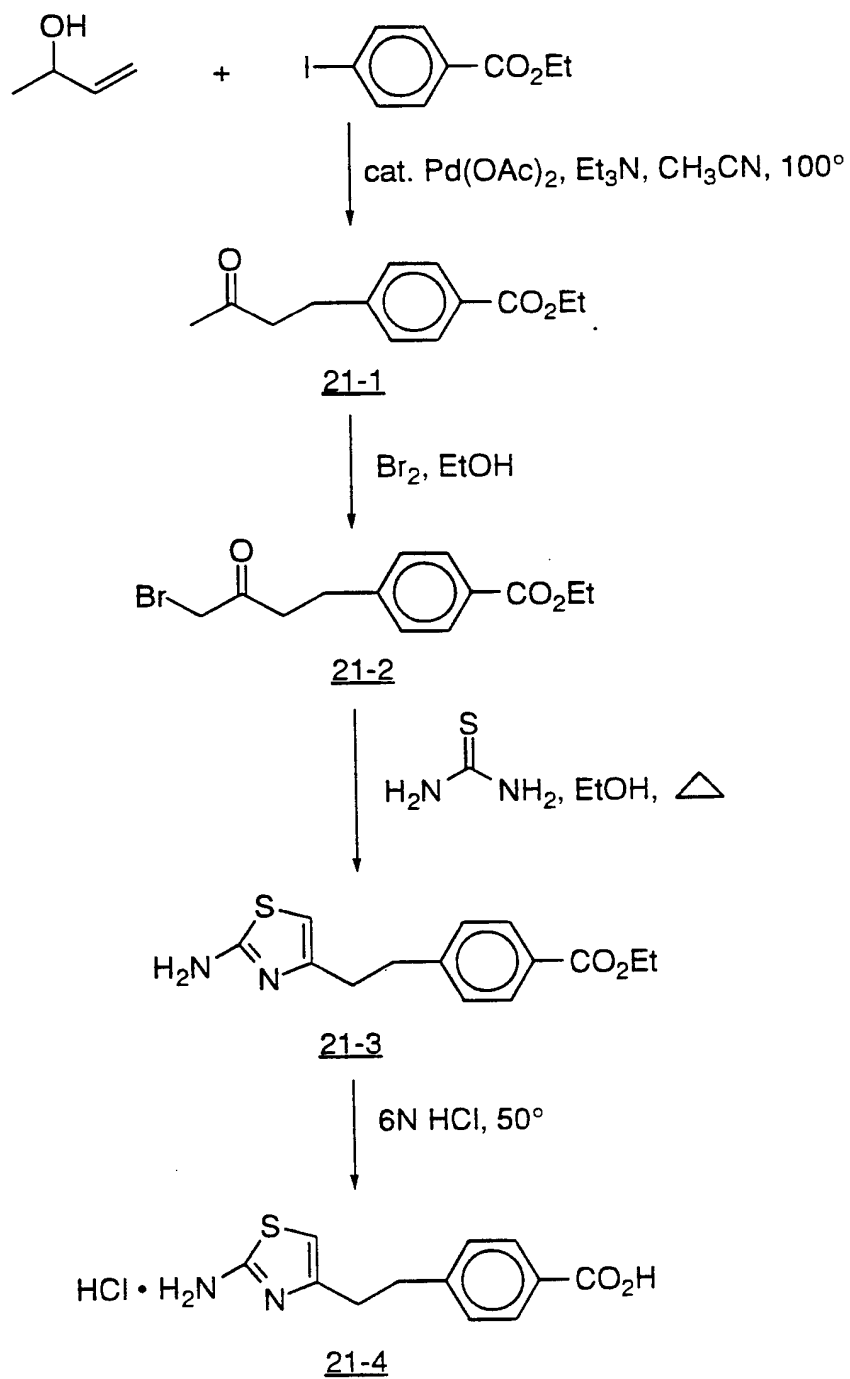
25 4-[2-[N-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]amino]-ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (20-4)

- A solution of 20-3 (298 mg, 1.0 mmol), 12-1 (222 mg, 0.5 mmol), DIPEA (261 μL, 1.5 mmol), H₂O (6 drops) and DMF (6 mL) was heated at 100°C for 24 h. The cooled solution was concentrated at 50°C and the residue chromatographed (silica, 9:0.5:0.5 ethanol/H₂O/NH₄OH) to give 20-4 as a colorless solid after lyophilization. TLC R_f=0.16 (silica, 9:0.5:0.5 ethanol/NH₄OH/H₂O);

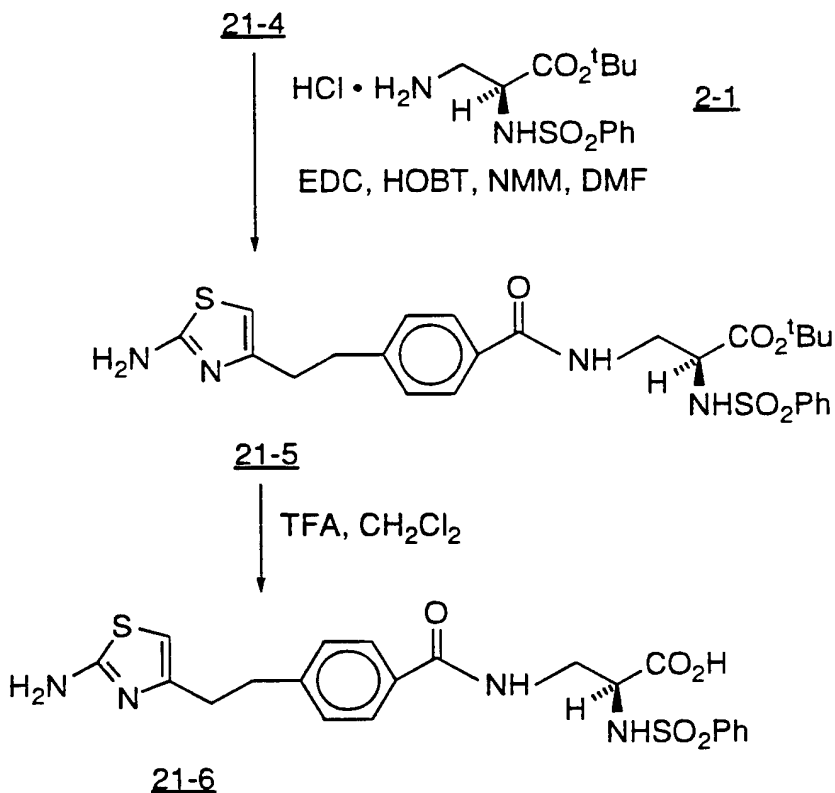
- 116 -

^1H NMR (300 MHz, CD_3OD) δ 7.83 (m, 2H), 7.77 (d, $J = 9$ Hz, 2H), 7.48 (m, 3H), 7.01 (d, $J = 9$ Hz, 2H), 4.19 (m, 3H), 3.91 (bs, 2H), 3.75-3.40 (m, 4H), 1.90-1.35 (m, 8H).

- 117 -

SCHEME 21

- 118 -

SCHEME 21 (CONT'D)5 Ethyl 4-(3-oxobut-1-yl)benzoate (21-1)

- 3-Hydroxy-1-butene (Aldrich) (2.15 mL, 25 mmol), ethyl 4-iodobenzoate (5.52 g, 20 mmol), Et₃N (3.5 mL, 25 mmol) and Pd(OAc)₂ (19 mg, 0.08 mmol) were combined in 6 mL CH₃CN, sealed in a glass pressure tube and heated at 100° for 3 h. The mixture was cooled, diluted with Et₂O, washed with water, 1N NaOH, 5% KHSO₄, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% EtOAc/hexanes) provided 21-1 as a white crystalline solid. R_f 0.41 (silica, 30% EtOAc/hexane).
- ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, J=8 Hz, 2H), 7.25 (d, J=8 Hz, 2H), 4.36 (q, J=7 Hz, 2H), 2.95 (t, J=7 Hz, 2H), 2.78 (t, J=7 Hz, 2H), 2.15 (s, 3H), 1.38 (t, J=7 Hz, 3H).

- 119 -

Ethyl 4-(4-bromo-3-oxobut-1-yl)benzoate (21-2)

21-1 (3.13 g, 14.2 mmol) was dissolved in EtOH (30 mL) at 0°, and Br₂ (805 µL, 15.6 mmol) was added. After warming to RT for 16 h the reaction was concentrated, diluted with Et₂O, washed with
5 water and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% EtOAc/hexane) provided 21-2 as a white solid. R_f 0.67 (silica, 30% EtOAc/hexane).

¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J=8 Hz, 2H), 7.26 (d, J=8 Hz, 2H), 4.36 (q, J=7 Hz, 2H), 3.85 (s, 2H), 3.00 (s, 4H), 1.38 (t, J=7 Hz,
10 3H).

Ethyl 4-[2-(2-aminothiazol-4-yl)ethyl]benzoate (21-3)

Thiourea (374 mg, 4.9 mmol) and 21-2 (1.4 g, 4.7 mmol) were combined in 24 mL EtOH and heated to reflux for 1 h.

15 Concentration and flash chromatography (silica, 80% EtOAc/hexane then 10% MeOH/EtOAc) provided 21-3 as a white solid. R_f 0.54 (silica, EtOAc).

¹H NMR (300 MHz, DMSO) δ 7.86 (d, J=8 Hz, 2H), 7.35 (d, J=8 Hz, 2H), 6.18 (s, 1H), 4.29 (q, J=7 Hz, 2H), 3.4 (br s), 2.95 (t, J=7 Hz, 2H),
20 2.73 (t, J=8 Hz, 2H), 1.31 (t, J=7 Hz, 3H).

4-[2-(2-Aminothiazol-4-yl)ethyl]benzoic acid hydrochloride (21-4)

Ester 21-3 (1.5 g, 5.43 mmol) was treated with 6N HCl for 16 h at RT then 16 h at 50°. Concentration provided 21-4 as an off-
25 white solid.

R_f 0.74 (silica, 9:1:1 CH₂Cl₂/MeOH/HOAc).

¹H NMR (300 MHz, DMSO) δ 9.45 (br s), 8.10 (d, J=8 Hz, 2H), 7.58 (d, J=8 Hz, 2H), 6.71 (s, 1H), 3.90 (br s), 3.20 (t, J=7 Hz, 2H), 3.07 (t, J=7 Hz, 2H).
30

4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine tert-butyl ester (21-5)

21-4 (150 mg, 0.53 mmol), amine hydrochloride 2-1 (0.53 mmol, 177 mg). HOBt (86 mg, 0.64 mmol), NMM (204 µL, 1.9

- 120 -

mmol), and EDC (122 mg, 0.64 mmol) were combined in 2.6 mL DMF at -15°, warmed to RT and stirred for 16 h. The reaction was diluted with EtOAc, washed with water, saturated NaHCO₃ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 70%

5 EtOAc/hexane) provided 21-5 as a clear oil.

R_f 0.48 (silica, EtOAc).

¹H NMR (300 MHz, CDCl₃) δ 7.86 (d, J=8 Hz, 2H), 7.69 (d, J=8 Hz, 2H), 7.60-7.45 (m, 3H), 7.24 (d, J=8 Hz, 2H), 6.70 (br m, 1H), 6.05 (s, 1H), 5.90 (br m, 1H), 4.92 (br s, 2H), 3.85-4.00 (m, 2H), 3.62 (m, 1H),
10 2.99 (t, J=8 Hz, 2H), 2.88 (t, J=8 Hz, 2H), 1.29 (s, 9H).

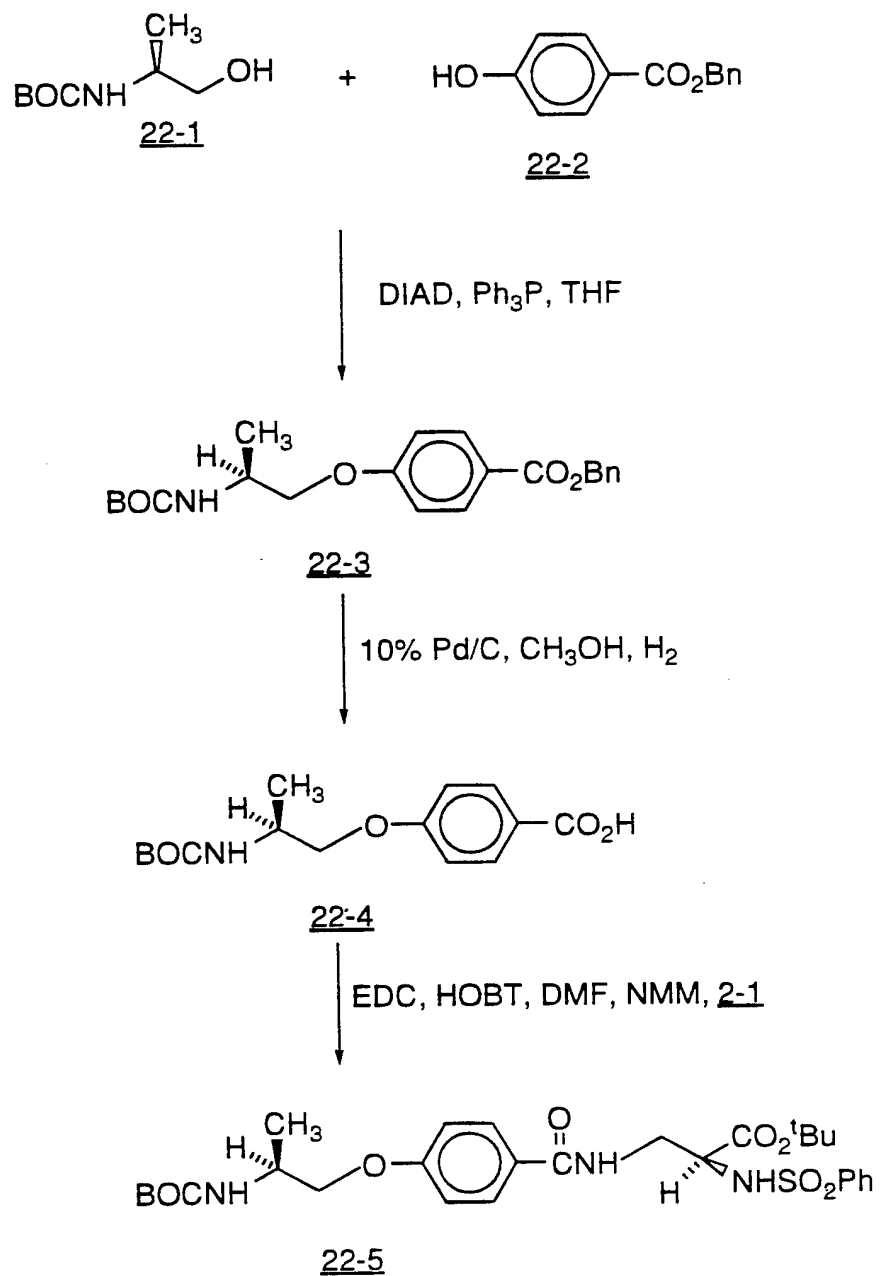
4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine (21-6)

Ester 21-5 (200 mg, 0.377 mmol) was dissolved in 2 mL
15 CH₂Cl₂, and 2 mL TFA was added. After 4 h at RT the mixture was concentrated, azeotroped with toluene, and purified by flash chromatography (silica, 28:10:1:1 EtOAc/EtOH/NH₄OH/H₂O) providing 21-6 as a white solid.

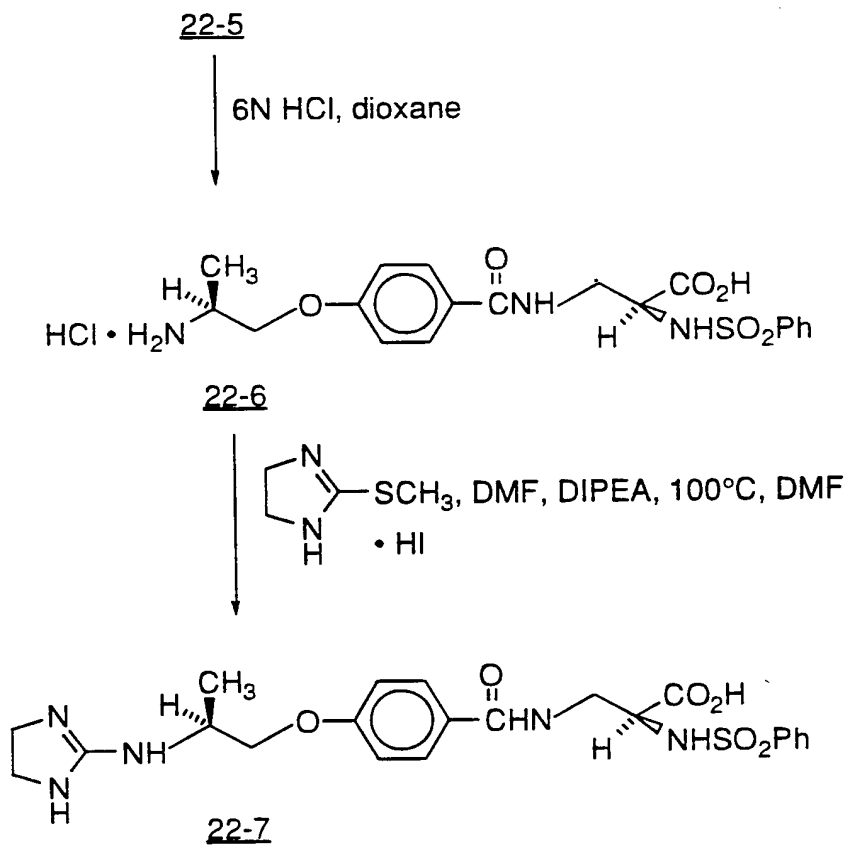
R_f 0.39 (silica, 12:10:1:1 EtOAc/EtOH/NH₄OH/H₂O).

20 ¹H NMR (400 MHz, DMSO) δ 8.6 (br s), 7.77 (d, J=8 Hz, 2H), 7.65 (d, J=8 Hz, 2H), 7.58 (t, J=7 Hz, 1H), 7.51 (t, J=7 Hz, 2H), 7.27 (d, J=8 Hz, 2H), 6.84 (m, 1H), 6.11 (s, 1H), 3.50-3.40 (m, 2H), 3.32 (br s), 2.92 (t, J=8 Hz, 2H), 2.70 (t, J=8 Hz, 2H).

- 121 -

SCHEME 22

- 122 -

SCHEME 22 (CONT'D)

- 123 -

Benzyl 4-[2(S)-(N-BOC-amino)propyloxy]benzoate (22-3)

- A THF (25 mL) solution of DIAD (2.9 mL, 14.8 mmol) and 22-1 (Fluka) (2.0 g, 11.4 mmol) was added dropwise to a stirred solution of THF (50 mL), 22-2 (Fluka) (2.6 g, 11.4 mmol) and Ph₃P (3.9 g, 14.8 mmol) over a 2 h period, followed by heating for 20 h at 70°C. The cooled reaction mixture was concentrated and purified by flash chromatography (silica, 20% EtOAc/hexanes) to give 22-3 as a colorless oil.
- TLC R_f 0.36 (silica, 5% acetone/CH₂Cl₂);
- ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, J=9 Hz, 2H), 7.70-7.30 (m, 5H), 6.92 (d, J=9 Hz, 2H), 6.45 (m, 1H), 5.33 (s, 2H), 4.75 (m, 1H), 4.06 (m, 1H), 3.96 (m, 2H), 1.45 (s, 9H), 1.26 (d, 3H).

4-[2(S)-(N-BOC-Amino)propyloxy]benzoic acid (22-4)

- A mixture of 22-3 (1.6 g, 4.3 mmol), 10% Pd/C (0.33 g) and ethanol (25 mL) was stirred under a hydrogen atmosphere (1 atm) for 20 h. Filtration through a celite pad followed by concentration of the filtrate gave 22-4 as a colorless solid.
- ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, J=9 Hz, 2H), 6.96 (d, J=9 Hz, 2H), 4.77 (m, 1H), 4.09 (m, 1H), 3.99 (m, 2H), 1.46 (s, 9H), 1.31 (d, J=7 Hz, 3H).

4-[2(S)-(N-BOC-Amino)propyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine tert-butyl ester (22-5)

- Following the procedure for coupling 19-6 to 2-1, 22-4 (295 mg, 1.0 mmol) was coupled to 2-1 (336 mg, 1.0 mmol) to give 22-5 as a beige solid.
- TLC R_f 0.28 (silica, 10% acetone/CH₂Cl₂);
- ¹H NMR (300 MHz, CDCl₃) δ 7.87 (m, 2H), 7.77 (d, J=9 Hz, 2H), 7.53 (m, 3H), 6.93 (d, J=9 Hz, 2H), 6.64 (m, 1H), 5.69 (m, 1H), 4.06 (m, 1H), 3.90 (m, 4H), 3.56 (m, 1H), 1.46 (s, 9H), 1.28 (s, 9H).

- 124 -

4-[2(S)-Aminopropoxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine
•HCl (22-6)

22-5 (545 mg, 0.94 mmol) in 6N HCl (25 mL) and dioxane (25 mL) was stirred overnight at ambient temperature. Concentration followed by trituration with ether gave 22-6 as a colorless solid.
TLC R_f 0.62 (silica, 95% ethanol/NH₄OH);
¹H NMR (300 MHz, CD₃OD) δ 7.83 (m, 2H), 7.79 (d, J=9 Hz, 2H), 7.48 (m, 3H), 7.08 (d, J=9 Hz, 2H), 4.3-3.3 (m, 6H), 1.43 (d, J=7 Hz, 3H).

10

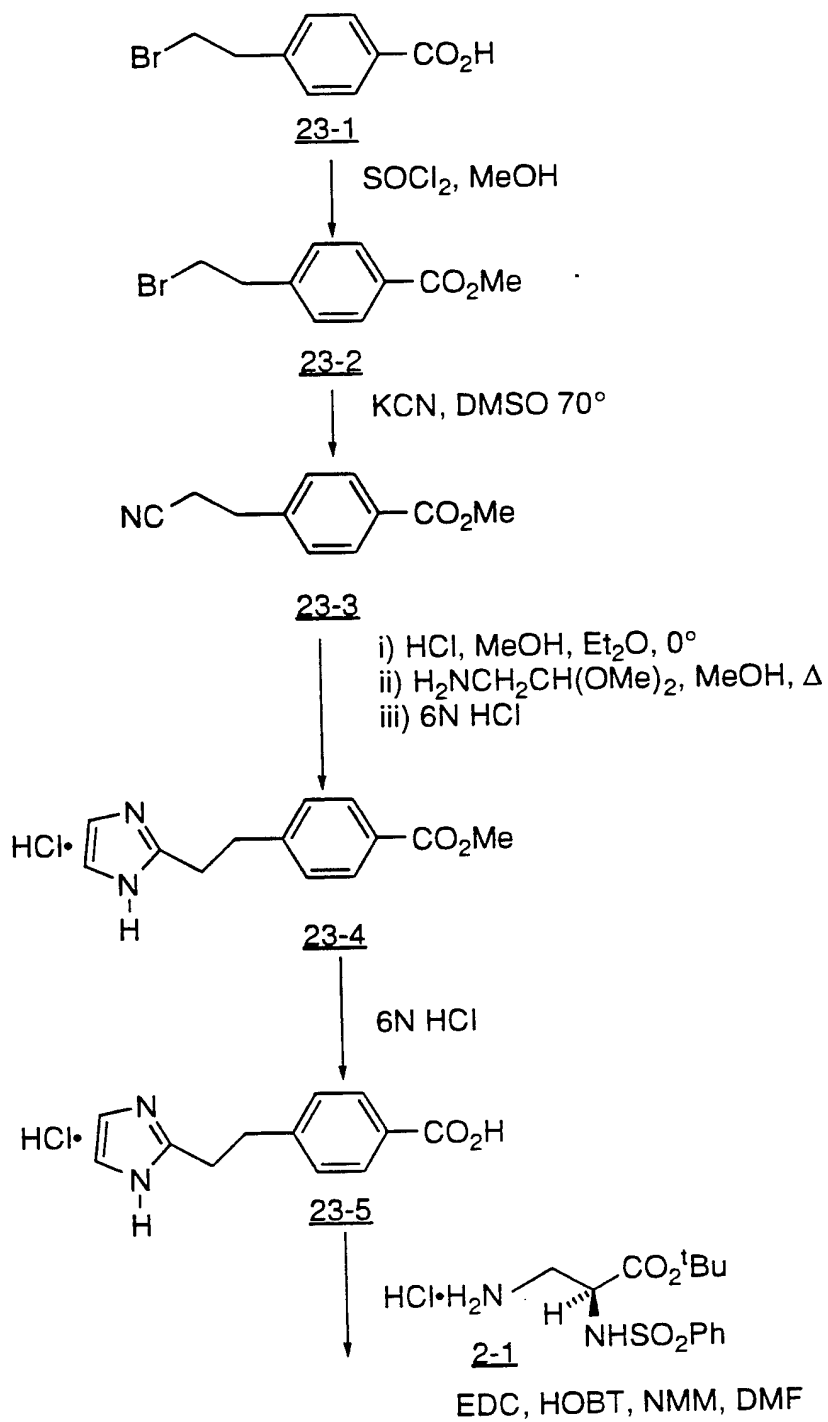
4-[2(S)-(N-(2-Imidazolin-2-yl)amino)propoxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine trifluoroacetate (22-7)

A mixture of 22-6 (256 mg, 0.51 mmol), DIPEA (292 μ L, 1.7 mmol), (2-methylthio-2-imidazoline•HI) (273 mg, 1.1 mmol) and DMF (2 mL) was heated at 100°C for 24 h. Concentration followed by flash chromatography (silica, 9:1:1:1 ethanol/NH₄OH/H₂O) gave a beige solid. This solid was purified on an HPLC semiprep (C18 column, 95:5 to 5:95 H₂O (0.1% TFA)/CH₃CN gradient) followed by lyophilization to give 22-7 as a colorless solid.
TLC R_f 0.33 (silica, 9:0.5:0.5 ethanol/H₂O/NH₄OH);
¹H NMR (300 MHz, CD₃OD) δ 7.83 (m, 2H), 7.76 (d, J=(9 Hz, 2H), 7.47 (m, 3H), 7.00 (d, J=9 Hz, 2H), 4.20-3.40 (m, 6H), 3.73 (m, 4H), 1.37 (d, J=7 Hz, 3H).

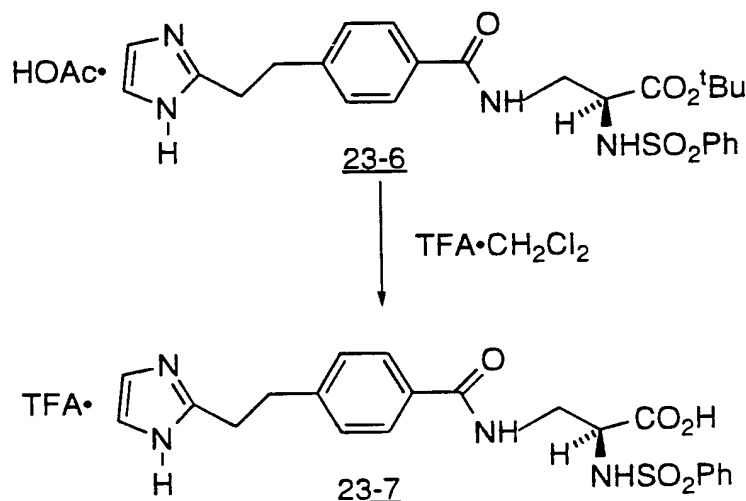
20

- 125 -

SCHEME 23



- 126 -

SCHEME 23 (CONT'D)Methyl 4-(2-bromoethyl)benzoate (23-2)

- 5 23-1 (1.95 g, 8.60 mmol) (Aldrich) was suspended in 50 mL MeOH and SOCl₂ (5.0 mL, 69 mmol) was added dropwise. Following an exothermic reaction, the mixture was stirred at RT for 16 h, concentrated, and purified by flash filtration (silica, 5% EtOAc/hexanes) providing 23-2 as a colorless oil. R_f 0.37 (silica, 10% EtOAc/hexanes).
- 10 ¹H-NMR (300 MHz, CDCl₃) δ 8.00 (d, J=8 Hz, 2H), 7.29 (d, J=8 Hz, 2H), 3.91 (s, 3H), 3.59 (t, J=7 Hz, 2H), 3.22 (d, J=7 Hz, 2H).

Methyl 4-(2-cyanoethyl)benzoate (23-3)

- 15 Bromide 23-2 (0.52 g, 2.14 mmol) and KCN (167 mg, 2.57 mmol) were combined in 10 mL DMSO. After 20 h, at RT and 1.5 h at 70° the reaction mixture was diluted with EtOAc, washed with water, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄), and concentrated providing 23-3 as a yellow solid. R_f 0.23 (30% EtOAc/hexanes).
- 20 ¹H-NMR (300 MHz, CDCl₃) δ 8.02 (d, J=8 Hz, 2H), 7.32 (d, J=9 Hz, 2H), 3.92 (s, 3H), 3.02 (t, J=7 Hz, 2H), 2.66 (t, J=7 Hz, 2H).

- 127 -

Methyl 4-[2-(imidazol-2-yl)ethyl]benzoate hydrochloride (23-4)

- Nitrile 23-3 (400 mg, 2.11 mmol) was dissolved in 10 mL Et₂O at 0° MeOH (289 µL, 4.2 mmol) was added, the mixture was saturated with anhydrous HCl. Once the white ppt. formed, the solvent was evaporated and replaced with MeOH (5 mL), cooled to 0°, and aminoacetaldehyde dimethylacetal (250 µL, 2.3 mmol) was added. The reaction was heated to reflux for 3 days then concentrated, diluted in 10 mL 6 N HCl and concentrated again providing 23-4 as a solid. R_f 0.16 (silica, 4:1:1 CH₂Cl₂/MeOH/HOAc).
- 10 ¹H-NMR (400 MHz, D₂O) δ 7.59 (d, J=7 Hz, 2H), 7.04 (d, J=7 Hz, 2H), 6.77 (m, 2H), 3.74 (bs, 2H), 2.89 (br s, 5H).

4-[2-(Imidazol-2-yl)ethyl]benzoic acid hydrochloride (23-5)

- Ester 23-4 (450 mg; 1.77 mmol) was dissolved in 6N HCl and stirred for 16 h. Concentration provided 23-5 as dark oil. R_f 0.28 (silica, 4:1:1 CH₂Cl₂/MeOH/HOAc).
- 15 ¹H-NMR (400 MHz, DMSO) δ 7.84 (d, J=8 Hz, 2H), 7.51 (s, 2H), 7.32 (d, J=7 Hz, 2H), 3.27 (t, J=7 Hz, 2H), 3.19 (t, J=7, 2H).

20 4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine tert-butyl ester acetate (23-6)

- Acid 23-5 (ca 2 mmol), amine 2-1 (700 mg, 2.0 mmol), HOBT (324 mg, 2.4 mmol), and NMM (0.77 mL, 7.0 mmol) were combined in 10 mL DMF at -15°, then EDC (364 mg, 1.9 mmol) was added. The mixture was warmed to RT, stirred overnight, then concentrated. Flash chromatography (silica, 4:1:1 CH₂Cl₂/MeOH/HOAc) provided 23-6, R_f 0.22 (silica, 4:1:1 CH₂Cl₂:MeOH:HOAc).
- 25

30 4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine trifluoroacetate (23-7)

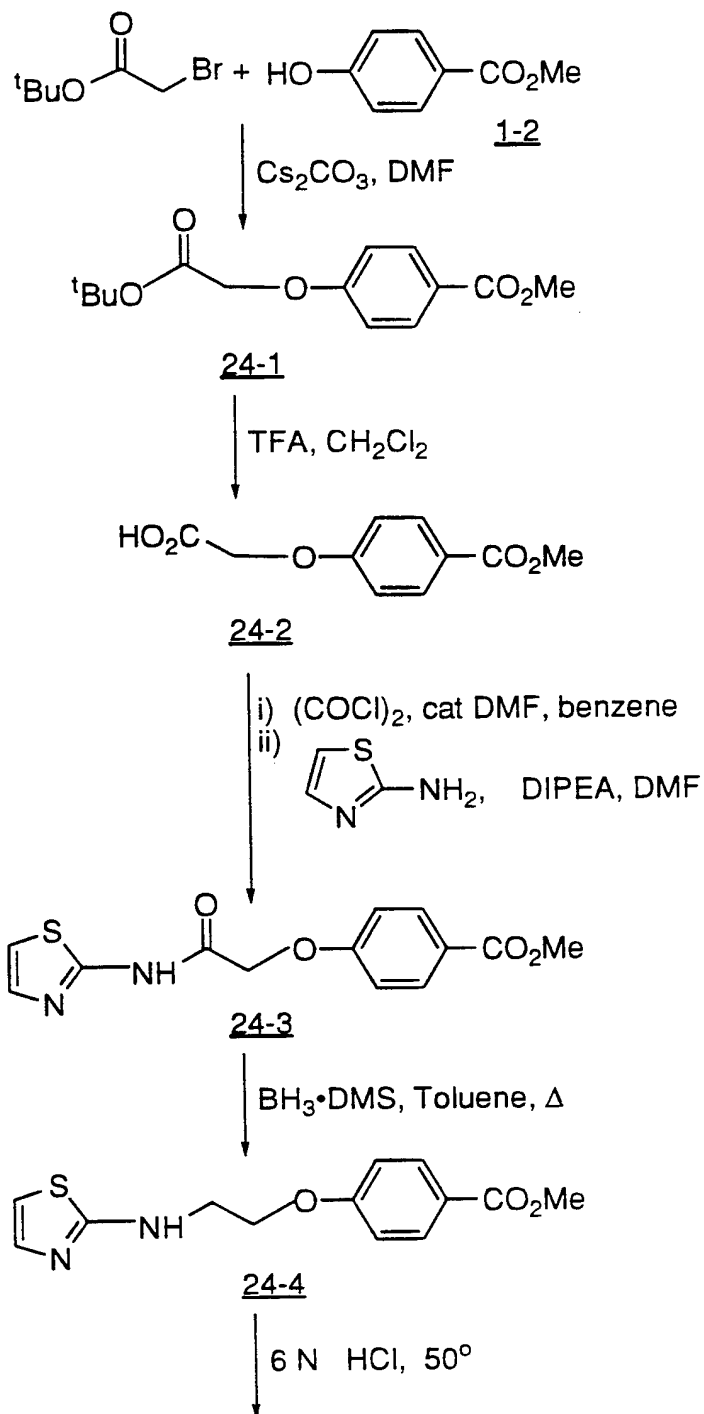
Ester 23-6 (100 mg, 0.2 mmol) was dissolved in 5 mL CH₂Cl₂, and 5 mL TFA was added. After 1 h the reaction was concentrated and azeotroped with toluene. Flash chromatography

- 128 -

(silica, 50:1:1 EtOH/NH₄OH/H₂O) and preparative HPLC (C₁₈, 0.1% TFA H₂O/CH₃CN) provided 23-7.

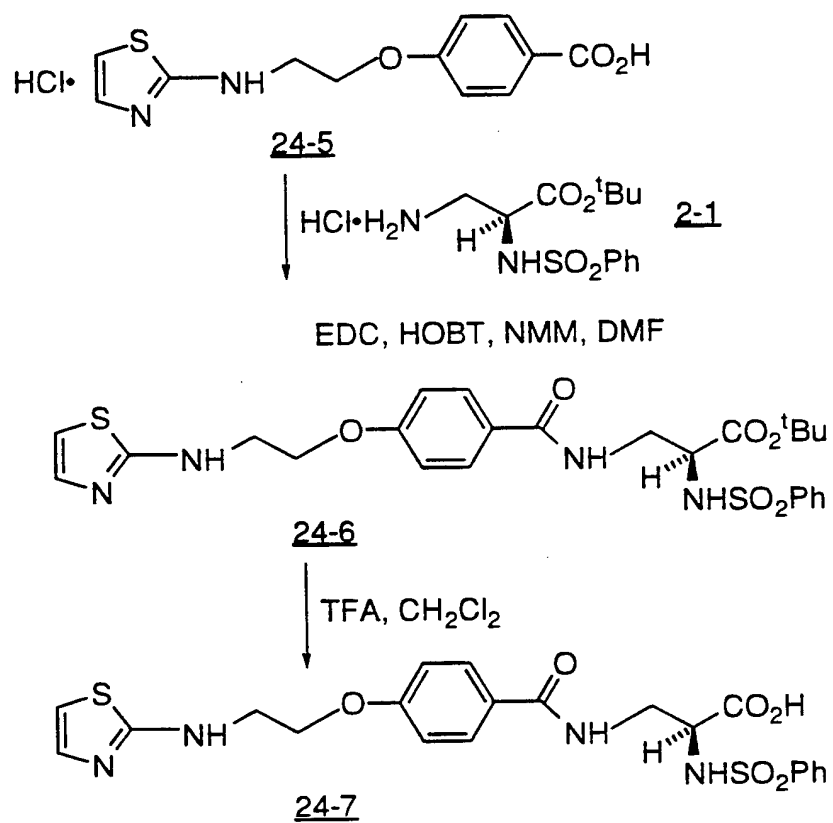
¹H-NMR (400 MHz, D₂O) δ 7.65 (d, J=7 Hz, 2H), 7.39 (d, J=8 Hz, 2H), 7.28-7.20 (m, 3H), 7.15 (s, 2H), 7.11 (d, J=9 Hz, 2H), 3.91 (dd, J=10, 4
5 Hz, 1H), 3.60 (dd, J=14, 4 Hz, 1H), 3.32 (dd, J=14, 10 Hz, 1H), 3.23 (t, J=7 Hz, 2H), 3.06 (t, J=7 Hz, 2H).

- 129 -

SCHEME 24

- 130 -

SCHEME 24 (CONT'D)



- 131 -

Methyl 4-(t-butyloxyacetyloxy)benzoate (24-1)

t-Butyl bromoacetate (0.83 mL, 5.1 mmol), methyl 4-hydroxybenzoate (780 mg, 5.1 mmol) and Cs₂CO₃ (1.83 g, 5.6 mmol) were combined in 25 mL DMF. After 16 h, the reaction was diluted with ethyl acetate, washed with water, saturated NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated providing 24-1 as a yellow oil. R_f 0.84 (silica, 50% EtOAc/hexane).

¹H-NMR (300 MHz, CDCl₃) δ 7.96 (d, J=8 Hz, 2H), 6.88 (d, J=8 Hz, 2H), 4.55 (s, 2H), 3.86 (s, 3H), 1.46 (s, 9H).

Methyl 4-(carboxymethyloxy)benzoate (24-2)

Ester 24-1 was dissolved in 15 mL CH₂Cl₂, then 15 mL TFA was added. After 2 h, the mixture was concentrated providing 24-2 as a white solid.

¹H-NMR (300 MHz, DMSO) δ 7.91 (d, J=9 Hz, 2H), 7.03 (d, J=9 Hz, 2H), 4.79 (s, 2H), 3.82 (s, 3H).

Methyl 4-[(thiazol-2-ylamino)acetyloxy]benzoate (24-3)

Acid 24-2 (1.0 g, 5 mmol) was suspended in 25 mL benzene, a few drops of DMF were added, then oxalyl chloride (1.3 mL, 15 mmol) in two portions. Once the gas evolution stopped, the homogeneous solution was concentrated, diluted with 25 mL DMF, and treated with 2-aminothiazole (550 mg, 5.5 mmol) and DIPEA (1 mL, 5.7 mmol). This mixture was stirred for 16 h, diluted with EtOAc, washed with water, sat. NaHCO₃, and brine, dried (MgSO₄) and concentrated providing 24-3 as an orange solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.06 (d, J=9 Hz, 2H), 7.50 (d, J=4 Hz, 1H), 7.05 (d, J=4 Hz, 1H), 7.00 (d, J=9 Hz), 4.80 (s, 2H), 3.91 (s, 3H).

Methyl 4-[2-(thiazol-2-ylamino)ethyloxy]benzoate (24-4)

Amide 24-3 (1.0 g, 3.4 mmol) was dissolved in 7 mL toluene at 0°, and BH₃•DMS (341 μL, 3.6 mmol) was added. After 15 min, the reaction was heated to reflux for 16 h, cooled to 0°, and quenched with 10% Na₂CO₃. The mixture was extracted with EtOAc,

- 132 -

the organic phase was washed with water and brine, dried (MgSO₄), concentrated, and purified by flash chromatography (silica, 70% EtOAc/hexane) providing 24-4 as a white solid. R_f 0.64 (silica, EtOAc).

- 5 ¹H-NMR (400 MHz, CDCl₃) δ 7.99 (d, J=9 Hz, 2H), 7.14 (d, J=4 Hz, 1H), 6.92 (d, J=9 Hz, 2H), 6.53 (d, J=4 Hz, 1H), 4.24 (t, J=5 Hz, 2H), 3.89 (s, 3H), 3.79 (q, J=5 Hz, 2H).

4-[2-(Thiazol-2-ylamino)ethyloxy]benzoic acid-hydrochloride (24-5)

- 10 Ester 24-4 (180 mg, 0.65 mmol) was heated at 50° in 6 mL 6 N HCl for 16 h, then concentrated providing 24-5 as a yellow solid. R_f 0.68 (silica, 9:1:1 CH₂Cl₂/MeOH/HOAc).

- 15 ¹H-NMR (300 MHz, CD₃OD) δ 7.96 (d, J=9 Hz, 2H), 7.30 (d, J=4 Hz, 1H), 7.00 (d, J=9 Hz, 2H), 6.97 (d, J=4 Hz, 1H), 4.34 (t, J=5 Hz, 2H), 3.89 (t, J=5 Hz, 2H).

4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine tert-butyl ester (24-6)

- 20 Acid 24-5 (160 mg, 0.60 mmol), amine 2-1 (215 mg, 0.60 mmol), EDC (140 mg, 0.73 mmol), HOBt (98 mg, 0.73 mmol), and NMM (235 μL, 2.1 mmol) were combined in 3 mL DMF at -15°. After stirring at RT for 16 h, the reaction was diluted with EtOAc, washed with water, sat. NaHCO₃ and brine, dried, concentrated, and purified by flash chromatography (silica, 70% EtOAc/hexane) providing 24-6 as an off-white solid. R_f 0.54 (silica, EtOAc).

- 25 ¹H-NMR (400 MHz, CDCl₃) δ 7.86 (d, J=8 Hz, 2H), 7.76 (d, J=9 Hz, 2H), 7.57 (t, J=8 Hz, 1H), 7.50 (t, J=8 Hz, 2H), 7.14 (d, J=4 Hz, 1H), 6.92 (d, J=9 Hz, 2H), 6.70 (br m, 1H), 6.53 (d, J=4 Hz, 1H), 4.21 (t, J=5 Hz, 2H), 3.95-3.85 (m, 2H), 3.77 (t, J=5 Hz, 2H), 3.58 (m, 1H),
30 1.28 (s, 9H).

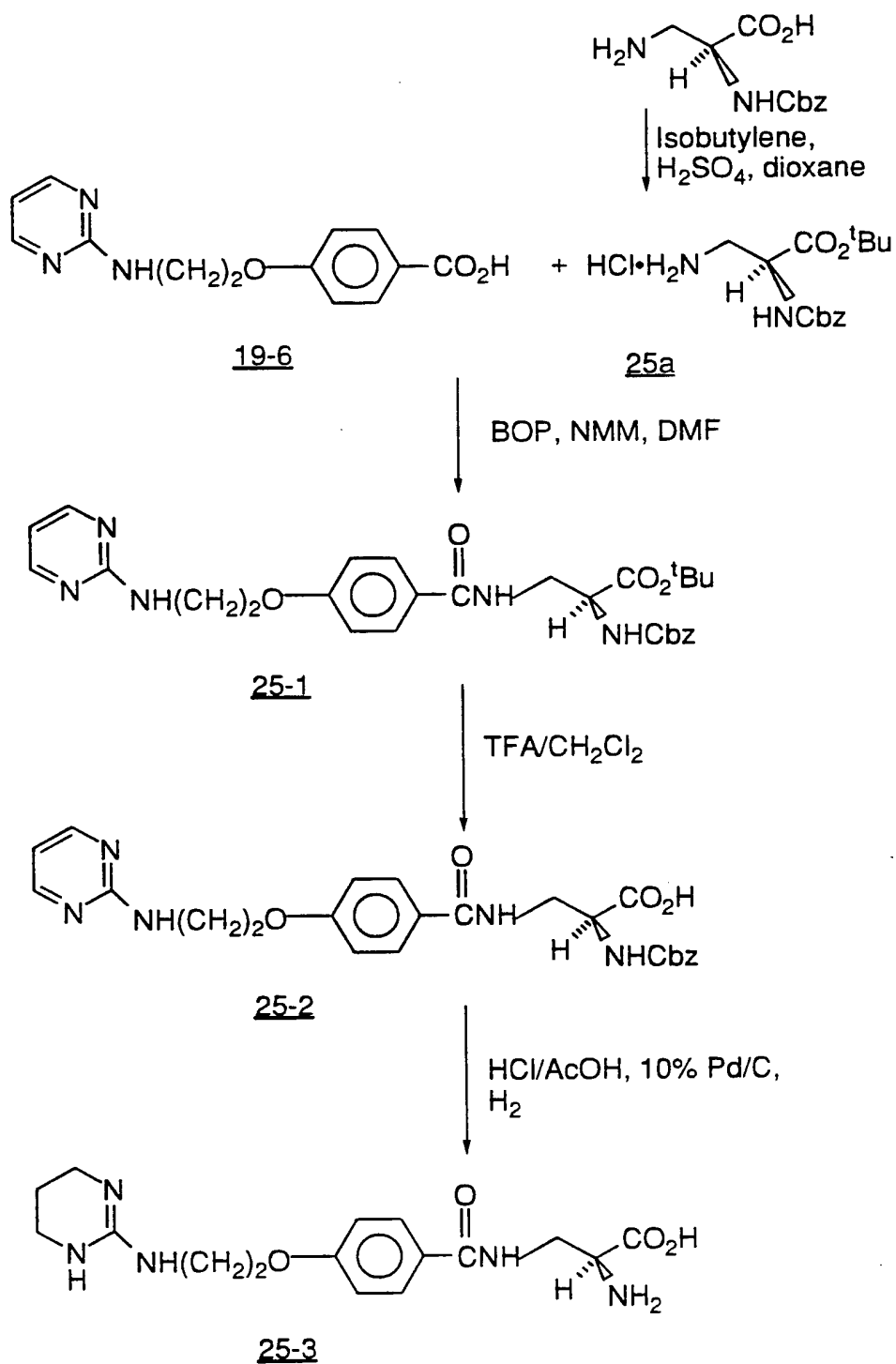
- 133 -

4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine (24-7)

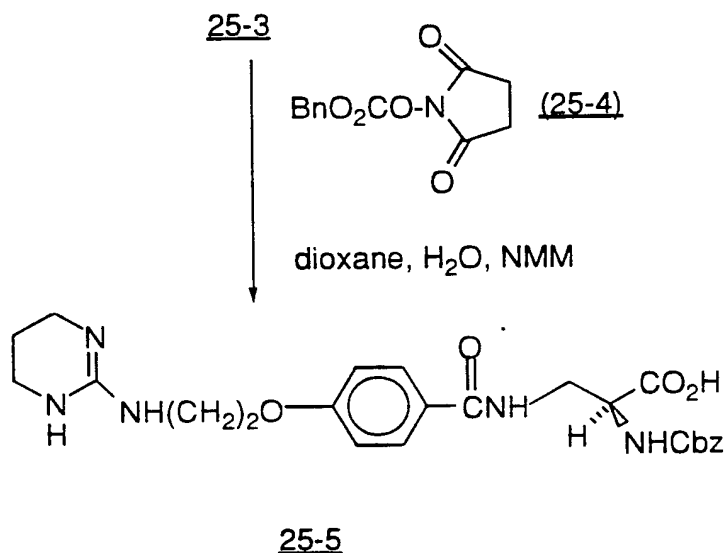
Ester 24-6 (197 mg, 0.36 mmol) was dissolved in 1.8 mL CH₂Cl₂ and treated with 1.8 mL TFA. Once the starting material had
5 disappeared, the reaction was concentrated, and flash chromatography (silica, 18:10:1:1 EtOAc/EtOH/NH₄OH/H₂O) provided 24-7 as a white solid. R_f 0.26 (silica, 18:10:1:1 EtOAc/EtOH/NH₄OH/H₂O).
¹H-NMR (400 MHz, D₂O) δ 7.52 (dd, J=8, 2 Hz, 2H), 7.41 (d, J=9 Hz, 2H), 7.10-7.04 (m, 3H), 6.93 (d, J=4 Hz, 1H), 6.89 (d, J=9 Hz, 2H),
10 6.53 (d, J=4 Hz, 1H), 4.21 (t, J= 5 Hz, 2H), 3.60 (t, J=5 Hz, 2H), 3.55-3.44 (m, 2H), 3.06 (dd, J=13, 9 Hz, 1H).

- 134 -

SCHEME 25



- 135 -

SCHEME 25 (CONT'D)

tert-Butyl 2(S)-Benzyloxycarbonylamino-3-aminopropionate
hydrochloride (25-a)

- 5 Following the procedure for converting 2-1b to 2-1, 3-amino-2(S)-benzyloxycarbonylamino-3-aminopropionic acid (230 mg, 1.0 mmol; Fluka) gave 25-a as a white solid.
¹H NMR (300 MHz, D₂O) δ 7.45 (br s, 5H), 5.18 (s, 2H), 4.35 (m, 1H), 3.35 (m, 1H), 3.05 (m, 1H), 1.45 (s, 9H).

10 4-[2-(Pyrimidin-2-ylamino)ethoxy]benzoyl-2(S)-benzyloxycarbonyl-amino-β-alanine tert-butyl ester (25-1)

- To a stirred solution of 19-6 (400 mg, 1.5 mmol), 25-a (538, 1.6 mmol), DMF (10 mL), and NMM (6.27 mg, 6.0 mmol) at
 15 ambient temperature was added BOP reagent (717 mg, 1.6 mmol).
 After 24 h, the reaction mixture was diluted with EtOAc and then washed with H₂O and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) gave 25-1 as a yellow oil.
 TLC R_f 0.14 (silica, 60% EtOAc/hexanes);
 20 ¹H NMR (300 MHz, CD₃OD) δ 8.22 (m, 2H), 7.68 (m, 2H), 7.24 (m, 5H), 6.92 (m, 2H), 6.06 (m, 1H), 5.00 (m, 2H), 4.30 (m, 1H), 4.13 (m, 2H), 3.72 (m, 2H), 3.67 (m, 2H), 1.32 (s, 9H).

- 136 -

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonyl-
amino- β -alanine (25-2)

A solution of 25-1 (840 mg, 1.6 mmol) and CH₂Cl₂ (10 ml) at ambient temperature was treated with TFA (10 ml). After
5 stirring for 4.0 h, the reaction mixture was concentrated and the residual TFA removed azeotropically with toluene. Trituration of the resulting waxy solid with ether provided 25-2 as a white solid.
1H NMR (300 MHz, CD₃OD) δ 8.41 (m, 2H), 7.67 (m, 2H), 7.22 (m, 5H), 6.91 (m, 2H), 6.82 (m, 2H), 4.98 (m, 2H), 4.38 (m, 1H), 4.20 (m,
10 2H), 3.83 (m, 2H), 3.72 (m, 1H), 3.62 (m, 1H).

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-
amino- β -alanine (25-3)

A mixture of 25-2 (500 mg, 1.0 mmol), conc. HCl (6 mL),
15 AcOH (30 mL) and 10% Pd/C (300 mg) was shaken on a Parr apparatus under a hydrogen atmosphere (70 psi) at ambient temperature for 3.0 h. The mixture was then filtered through a celite pad, the filtrate concentrated and the residual AcOH removed azeotropically with toluene. The residue was triturated with 8:1:1 ethanol/NH₄OH/H₂O.
20 The solid was collected by filtration, washed with ether and dried in vacuo to give 25-3 as a yellow solid. TLC R_f 0.17 (silica, 8:1:1 ethanol/NH₄OH/H₂O);
1H NMR (300 MHz, CD₃OD) δ 7.84 (d, J=9 Hz, 2H), 7.02 (d, J=9 Hz, 2H), 4.22 (m, 1H), 4.12 (m, 2H), 4.00-3.30 (m, 8H), 1.92 (m, 2H).

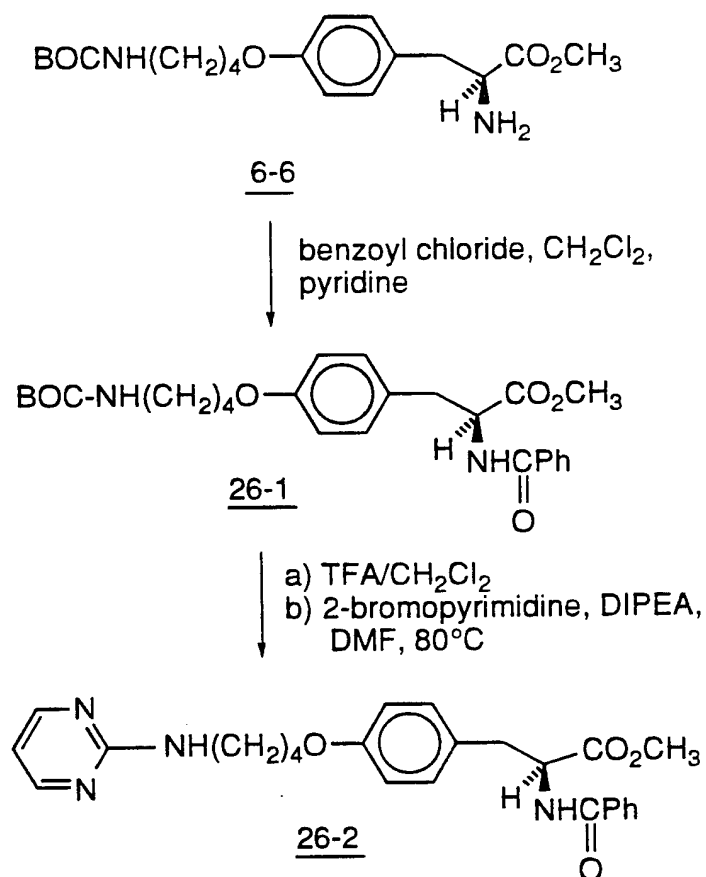
25 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino- β -alanine (25-5)

A stirred solution of 25-3 (360 mg, 1.0 mmol), dioxane (5 mL), H₂O (5 mL) and NMM (453 μ L, 4.0 mmol) at ambient
30 temperature was treated with 25-4 (Aldrich) (257 mg, 1.0 mmol). After 1.0 h the solution was concentrated. Flash chromatography (silica, 10:1:1 ethanol/NH₄OH/H₂O) gave 25-5 as a white solid. TLC R_f 0.34 (silica, 10:1:1 ethanol/NH₄OH/H₂O);

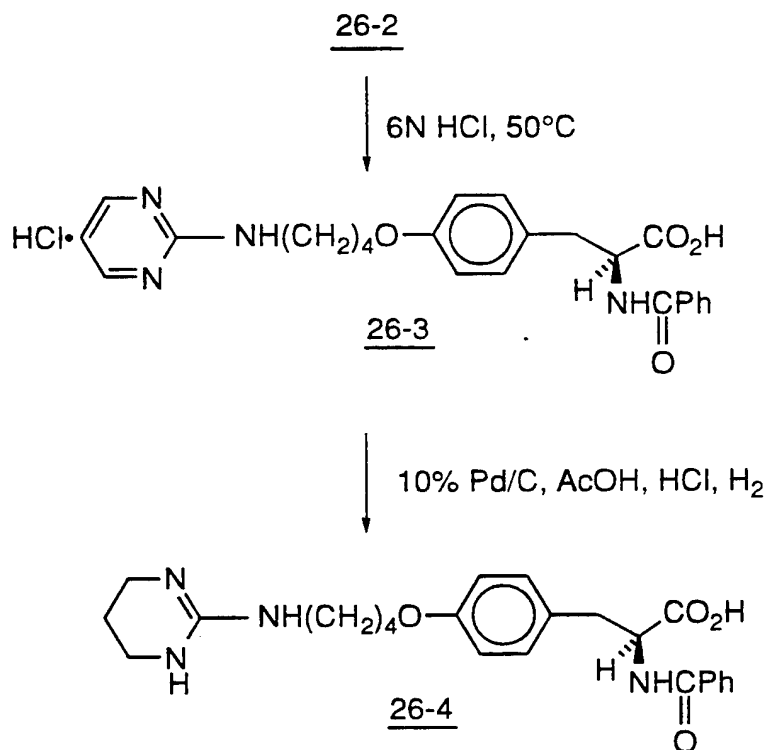
- 137 -

^1H NMR (300 MHz, $\text{DCI}/\text{CD}_3\text{OD}$) δ 7.80 (d, $J=9$ Hz, 2H), 7.31 (m, 5H), 7.02 (d, $J=9$ Hz, 2H), 5.07 (m, 2H), 4.50 (m, 1H), 4.19 (m, 2H), 3.77 (m, 2H), 3.62 (m, 2H), 3.38 (m, 4H), 1.97 (m, 2H).

5

SCHEME 26

- 138 -

SCHEME 26 (CONT'D)

5 Methyl 2(S)-benzoylamino-3-[4-(4-N-Boc-aminobutyloxy)phenyl]-
propionate (26-1)

A solution of 6-6 (600 mg, 1.6 mmol), pyridine (265 μ L, 3.3 mmol) and CH_2Cl_2 (10 mL) at ambient temperature was treated with benzoyl chloride (228 μ L, 2.0 mmol). After 24 h the solution was diluted with EtOAc and washed with H_2O , sat. NaHCO_3 , 10% KHSO_4
 10 and brine, dried (MgSO_4) and concentrated. Flash chromatography (silica, 30% EtOAc/hexanes) gave 26-1 as a white solid.
 TLC R_f 0.15 (silica, 30% EtOAc/hexanes);
 ^1H NMR (300 MHz, CD_3OD) δ 7.65 (m, 2H), 7.39 (m, 3H), 7.07 (m, 2H), 6.76 (m, 2H), 4.05 (m, 1H), 3.88 (m, 2H), 3.66 (s, 3H), 3.20-2.90
 15 (m, 4H), 1.80-1.50 (m, 4H), 1.39 (s, 9H).

- 139 -

Methyl 2(S)-benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)-phenyl]propionate (26-2)

A solution of 26-1 (375 mg, 0.8 mmol), CH₂Cl₂ (4 mL) and TFA (4 mL) was stirred at ambient temperature for 2.0 h. The solution was concentrated and the residual TFA removed azeotropically with toluene. The residue was dissolved in DMF (4 mL) then treated sequentially with DIPEA (414 µL, 3.2 mmol) and 2-bromopyrimidine (152 mg, 0.95 mmol) and then heated at 80°C for 20 h. The cooled reaction mixture was diluted with EtOAc and then washed with H₂O and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 50% to 80% EtOAc/hexanes) gave 26-2 as a brown oil. TLC R_f 0.34 (silica, 80% EtOAc/hexanes);
¹H NMR (300 MHz, CD₃OD) δ 8.17 (m, 2H), 7.68 (d, J=9 Hz, 2H), 7.40 (m, 3H), 7.09 (m, 2H), 6.76 (d, J=9 Hz, 2H), 6.49 (m, 1H), 4.05 (m, 1H), 3.90 (m, 3H), 3.68 (s, 3H), 3.40, 2.90 (m, 4H), 1.72 (m, 4H).

2(S)-Benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)phenyl]-propionic acid hydrochloride (26-3)

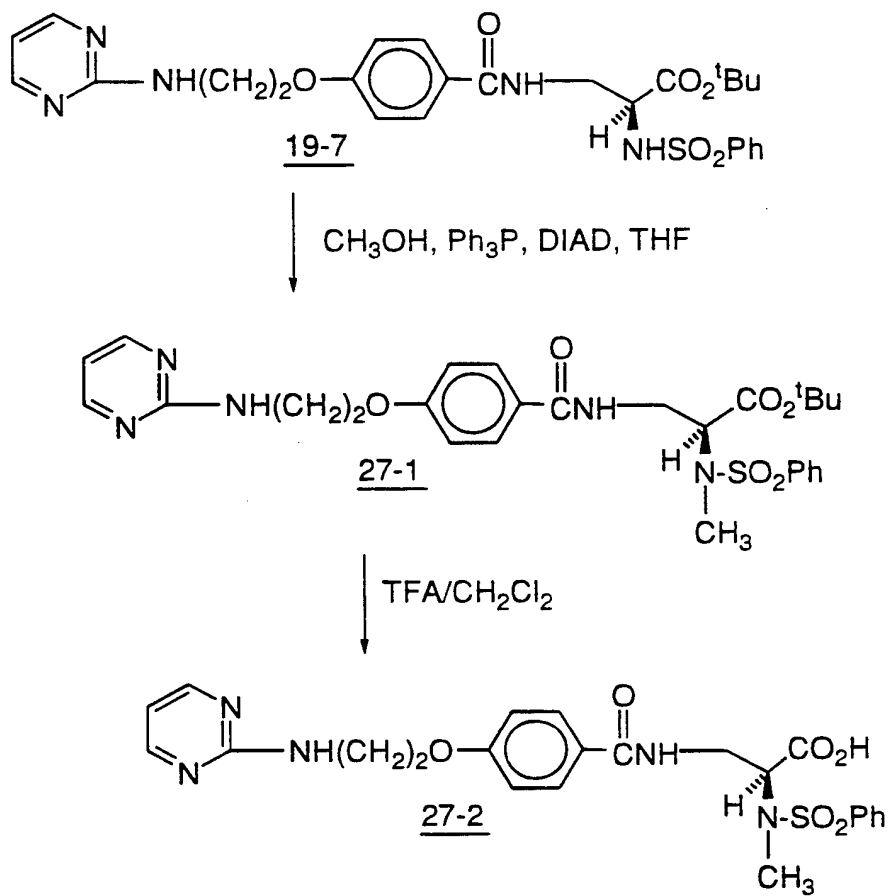
A solution of 26-2 (250 mg, 0.56 mmol), in 6N HCl (6 mL) was heated at 60°C for 2.0 h. The solution was concentrated to give 26-3 as a solid, which was used directly in the next step.

2(S)-Benzoylamino-3-[4-(4-(3,4,5,6-tetrahydropyrimidin-2-ylamino)-butyloxy)phenyl]propionic acid (26-4)

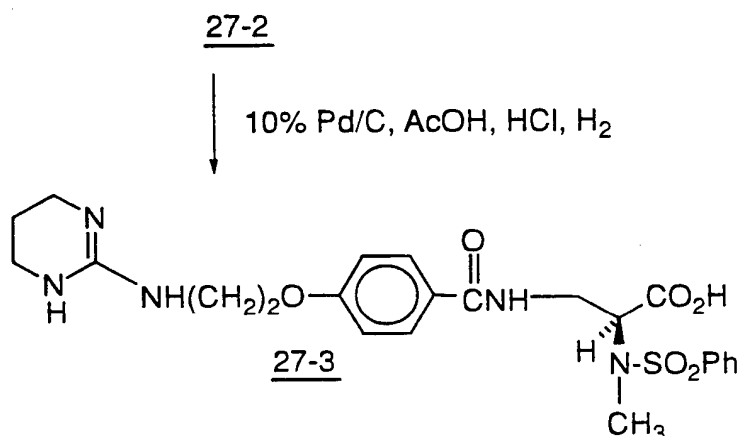
A mixture of 26-3 (250 mg, 0.56 mmol), AcOH (20 mL), conc. HCl (3 mL) and 10% Pd/C (150 mg) was shaken on the Parr apparatus (60 psi) at ambient temperature for 2.5 h. The reaction mixture was then filtered through a celite pad and the filtrate concentrated. Flash chromatography (silica, 10:1:1 to 9:1:1 ethanol/NH₄OH/H₂O) gave 26-4 as a white solid. TLC R_f (silica, 9:1:1 ethanol/NH₄OH/H₂O);
¹H NMR (400 MHz, CD₃OD) δ 7.78 (m, 2H), 7.60-7.40 (m, 3H), 7.17 (d, J=9 Hz, 2H), 6.79 (d, J=9 Hz, 2H), 4.70 (m, 1H), 3.96 (m, 2H), 3.33

- 140 -

(m, 4H), 3.30 (m, 1H), 3.16 (m, 2H), 3.11 (m, 1H), 1.95 (m, 2H), 1.80 (m, 2H), 1.73 (m, 2H).

SCHEME 27

- 141 -

SCHEME 27 (CONT'D)

4-[2-(Pyrimidin-2-ylamino)ethoxy]benzoyl-2(S)-(N-methyl)-
phenylsulfonylamino- β -alanine tert-butyl ester (27-1)

- 5 A solution of 19-7 (190 mg, 0.35 mmol), CH₃OH (28 μ L, 0.7 mmol), Ph₃P (101 mg, 0.39 mmol), DIAD (758 μ L, 0.9 mmol) and THF (10 mL) was stirred for 24 h at ambient temperature. The reaction mixture was then diluted with EtOAc and washed with H₂O and brine, dried (MgSO₄) and concentrated. Flash chromatography
- 10 (silica, CHCl₃ saturated with NH₃) gave crude 27-1 as a gum. TLC R_f=0.21 (silica, 20% acetone/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.29 (d, J=5 Hz, 1H), 7.90-7.40 (m, 10H), 6.90 (d, J=9 Hz, 2H), 6.57 (m, 1H), 4.72 (m, 1H), 4.19 (m, 2H), 3.87 (m, 2H), 2.90 (s, 3H), 1.30 (s, 9H).

- 15 4-[2-(Pyrimidin-2-ylamino)ethoxy]benzoyl-2(S)-(N-methyl)-phenylsulfonylamino- β -alanine (27-2)

- A solution of 27-1 (190 mg, 0.35 mmol), TFA (4 mL) and CH₂Cl₂ (8 mL) was stirred at ambient temperature for 4 h. The
- 20 reaction was concentrated and the residual TFA removed azeotropically with toluene. Flash chromatography (silica, 95/2.5/2.5 CH₂Cl₂/CH₃OH/AcOH) gave 27-2 as a colorless foam. TLC R_f=0.26 (silica, 9:0.5:0.5 CH₂Cl₂/CH₃OH/AcOH);

- 142 -

¹H NMR (300 MHz, CD₃OD) δ 8.30 (d, J=5 Hz, 2H), 7.74 (d, J=11 Hz, 2H), 7.71 (d, J=9 Hz, 2H), 7.45-7.25 (m, 3H), 6.99 (d, J=9 Hz, 2H), 6.62 (m, 1H), 5.80 (m, 1H), 4.21 (m, 2H), 3.90 (m, 1H), 3.79 (m, 2H), 3.60 (m, 1H), 2.89 (s, 3H).

5

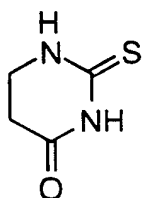
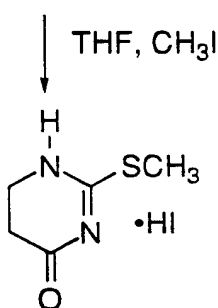
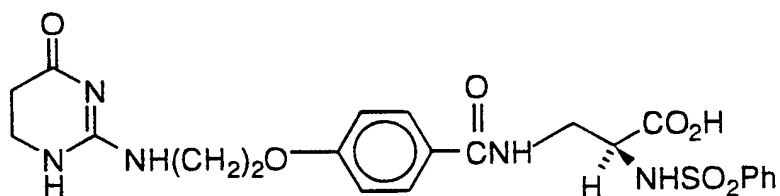
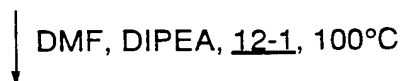
4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-
(N-methyl)phenylsulfonylamino-β-alanine (27-3)

A mixture of 27-2 (190 mg, 0.35 mmol), HOAc (10 mL),
conc. HCl (0.6 mL) and 10% Pd/C (38 mg) was shaken on the Parr
10 apparatus (40 psi) at ambient temperature for 2.0 h. The reaction
mixture was filtered through a celite pad and the filtrate concentrated.
Flash chromatography (silica, ethanol/NH₄OH/H₂O 9:0.5:0.5) gave 27-3
as a colorless lyophilizate.

TLC R_f 0.34 (silica, 8:1:1 ethanol/NH₄OH/H₂O);

15 ¹H NMR (300 MHz, CDCl₃) δ 7.80 (m, 4H), 7.55-7.35 (m, 3H), 7.02
(d, J=9 Hz, 2H), 7.02 (d, J=9 Hz, 2H), 4.95 (m, 1H), 4.20 (m, 2H), 3.86
(m, 1H), 3.69 (m, 1H), 3.59 (m, 2H), 3.38 (m, 4H), 2.88 (s, 3H), 1.95
(m, 2H)

- 143 -

SCHEME 2828-1 (Indian J. Chem., 1969, 7, 772)28-228-3(5,6-Dihydro-4-keto-(1H)-pyrimidin-2-yl)methylsulfide (28-2)

- A suspension of 28-1 (1.98 g, 15.2 mmol) in THF (40 mL) was treated with iodomethane and stirred at ambient temperature for 60 h. The heterogeneous reaction mixture was then filtered to give 28-2 as a colorless crystalline solid m.p. = 205°C (D).
¹H NMR (300 MHz, CD₃OD) δ 3.90 (t, J=7 Hz, 2H), 2.91 (t, J=7 Hz, 2H), 2.77 (s, 3H).

- 144 -

4-[2-(N-(5,6-Dihydro-4-keto-1(H)-pyrimidin-2-yl)amino)ethyloxy]-
benzoyl-2(S)-phenylsulfonylamino- β -alanine (28-3)

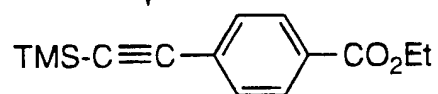
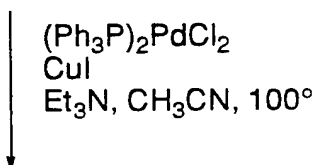
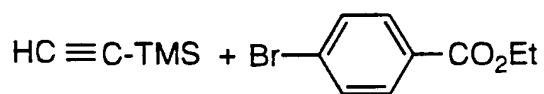
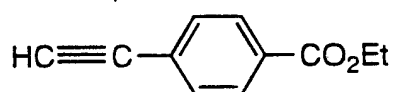
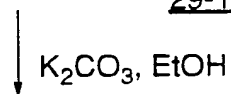
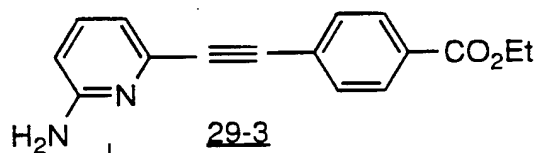
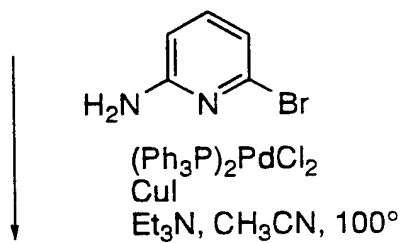
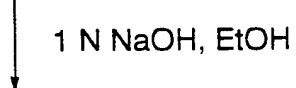
A solution of 28-2 (272 mg, 1.0 mmol), 12-1 (222 mg, 0.5 mmol), DIPEA (261 μ L, 1.5 mmol) and DMF (5 mL) was heated at
5 100°C for 20 h. The cool reaction mixture was concentrated.

Flash chromatography (silica, 95% ethanol/NH₄OH) and preparative HPLC (C18, 0.1% TFA in H₂O/CH₃CN) provided pure 28-3 as a colorless solid after lyophilization.

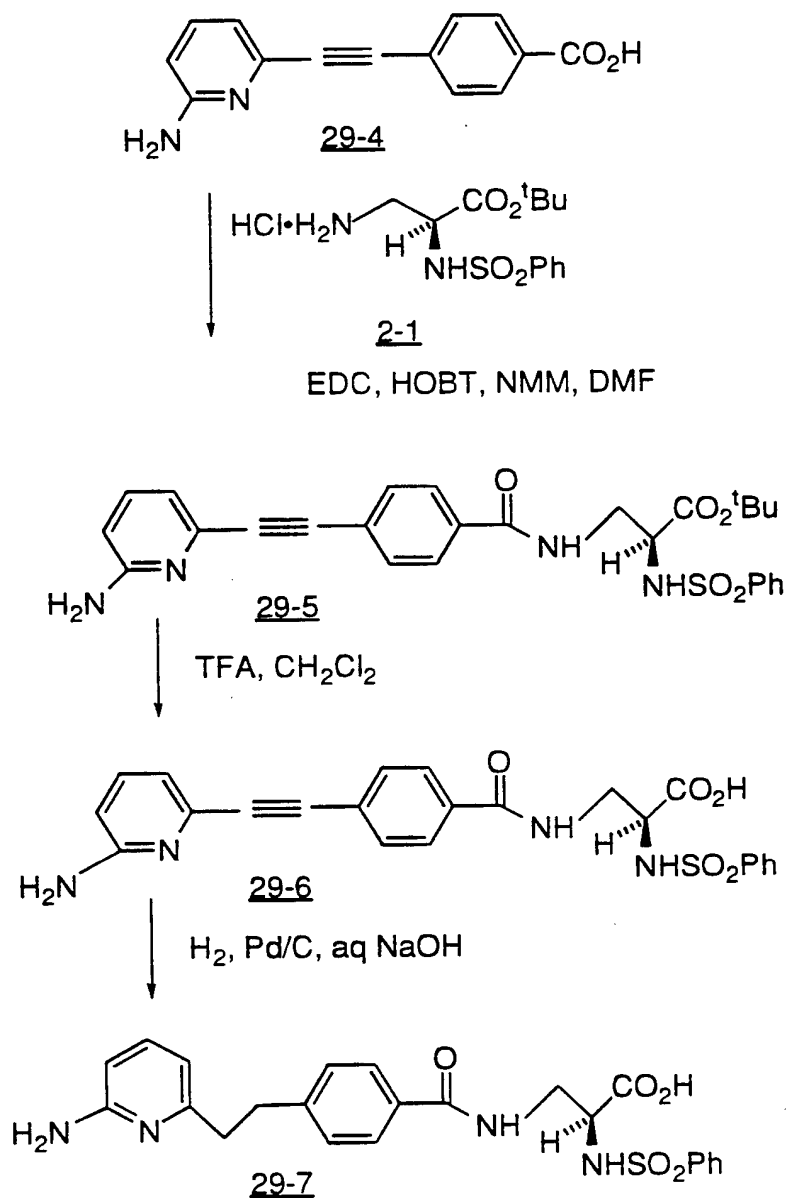
TLC R_f 0.58 (silica, 95% ethanol/NH₄OH);

10 ¹H NMR (300 MHz, CD₃OD) δ 7.83 (d, J=7 Hz, 2H), 7.78 (d, J=9 Hz, 2H), 7.48 (m, 3H), 7.02 (d, J=9 Hz, 2H), 4.26 (m, 2H), 4.20 (m, 1H), 3.80-3.60 (m, 4H), 3.48 (m, 1H), 2.76 (t, J=7 Hz, 2H).

- 145 -

SCHEME 2929-129-229-3

- 146 -

SCHEME 29 (CONT'D)Ethyl 4-(trimethylsilylethynyl)benzoate (29-1)

5

TMS-acetylene (Aldrich) (5.0 mL, 35.5 mmol), ethyl 4-bromobenzoate (58 mL, 35.5 mmol) and Et₃N (20 mL, 144 mmol) were combined in 50 mL CH₃CN in a glass pressure tube. (Ph₃P)₂PdCl₂ (198 mg, 0.28 mmol) and CuI (100 mg, 0.53 mmol)

- 147 -

were added, and the reaction was sealed and heated at 100° for 18 h. Dilution with EtOAc, washing twice with water, then brine, drying and concentration provided 29-1 as a brown liquid.

R_f 0.60 (silica, 10% EtOAc/hexane).

- 5 ¹H NMR (300 MHz, CDCl₃) δ 7.97 (d, J=8 Hz, 2H), 7.51 (d, J=9 Hz, 2H), 4.37 (q, J=7 Hz, 2H), 1.40 (t, J=7 Hz, 3H), 0.26 (s, 9H).

Ethyl-4-ethynylbenzoate (29-2)

- 10 Silylacetylene 29-1 (9.40 g, 38 mmol) was dissolved in 100 mL EtOH, K₂CO₃ (0.25 g 1.8 mmol) was added and the mixture was stirred for 16 h, concentrated, and purified by flash chromatography (silica, 5% Et₂O/hexane) provided 29-2 as a yellow oil.

R_f 0.47 (silica, 10% EtOAc/hexane).

- 15 ¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, J=8 Hz, 2H), 7.55 (d, J=8 Hz, 2H), 4.38 (q, J=7 Hz, 2H), 3.22 (s, 1H), 1.40 (t, J=7 Hz, 3H).

Ethyl 4-(2-aminopyridin-6-ylethynyl)benzoate (29-3)

- 20 2-Amino-6-bromopyridine (0.38 g, 2.4 mmol), alkyne 29-2 (0.35 g, 2.0 mmol), Et₃N (1.0 mL, 7.2 mmol), (Ph₃P)₂PdCl₂ (76 mg, 0.11 mmol), an CuI (26 mg, 0.14 mmol) were combined in 5 mL CH₃CN, sealed in a glass pressure tube and heated to 100° for 3 h. The mixture was diluted with EtOAc, washed with water and brine, dried (MgSO₄), concentrated, and purified by flash chromatography (silica, 5% acetone/hexane), to give 29-3 as a tan solid.

- 25 R_f 0.45 (silica, 10% acetone/hexane).

¹H NMR (300 MHz, CDCl₃) δ 8.03 (d, J=8 Hz, 2H), 7.64 (d, J=8 Hz, 2H), 7.44 (t, J=8 Hz, 1H), 6.95 (d, J=7 Hz, 1H), 6.50 (d, J=8 Hz, 1H), 4.55 (br s, 2H), 4.39 (q, J=7 Hz, 2H), 1.40 (t, J=7 Hz, 3H).

4-(2-Aminopyridin-6-ylethynyl)benzoic acid (29-4)

- 30 Ester 29-3 (300 mg, 1.13 mmol) and 1N NaOH (2.8 mL, 2.8 mmol) were combined in 6 mL EtOH. After 16 h the mixture was concentrated, EtOAc was added, and water and 10% KHSO₄ were added to pH 7. The resulting precipitate was collected, the organic

- 148 -

phase was washed with brine, dried and concentrated. Both fractions contained 29-4, an orange/yellow solid.

R_f 0.50 (silica, 18:1:1 CH₂Cl₂/MeOH/HOAc).

¹H NMR (400 MHz, CD₃OD + NaOD) δ 7.95 (d, J=9 Hz, 2H), 7.53 (d, J=9 Hz, 2H), 7.46 (dd, J=9,7 Hz, 1H), 6.84 (dd, J=7,1 Hz, 1H), 6.58 (dd, J=8,1 Hz, 1H).

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonyl-amino-β-alanine t-butyl ester (29-5)

10 Acid 29-4 (234 mg, 0.98 mmol), amine 2-1 (351 mg, 0.98 mmol), EDC (225 mg, 1.2 mmol), HOBT (159 mg, 1.2 mmol) and NMM (323 μL, 2.9 mmol) were combined in 5 mL DMF. After 16 h the mixture was diluted with EtOAc, washed with water, sat. NaHCO₃ and brine, dried (MgSO₄), concentrated and chromatographed (silica, 15 80% EtOAc/hexane) providing 29-5.

R_f 0.53 (EtOAc, silica).

¹H NMR (300 MHz, CDCl₃) δ 7.86 (d, J=8 Hz, 2H), 7.76 (d, J=9 Hz, 2H), 7.62 (d, J=9 Hz, 2H), 7.57-7.41 (m, 4H), 6.95 (dd, J=7,1 Hz, 1H), 6.86 (br m, 1H) 6.50 (dd, J=8, 1H, 1H), 5.92 (br m, 1H), 4.58 (br s, 20 2H), 4.00-3.84 (m, 2H), 3.62 (m, 1H), 1.29 (s, 9H).

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino-β-alanine (29-6)

25 Ester 29-5 (375 mg, 0.72 mmol), was dissolved in 3.6 mL CH₂Cl₂/3.6 mL TFA. After 2 h the reaction was concentrated, azeotroped with toluene, and triturated with 10:1:1 EtOH/NH₄OH/H₂O, providing 29-6 as a light yellow solid.

¹H NMR (400 MHz, D₂O + NaOD) δ 7.55-7.45 (m, 4H), 7.45-7.36 (m, 3H), 7.10-7.05 (m, 3H), 6.86 (m, 1H), 6.54 (m, 1H), 3.54-3.42 (m, 2H), 30 3.04 (m, 1H).

- 149 -

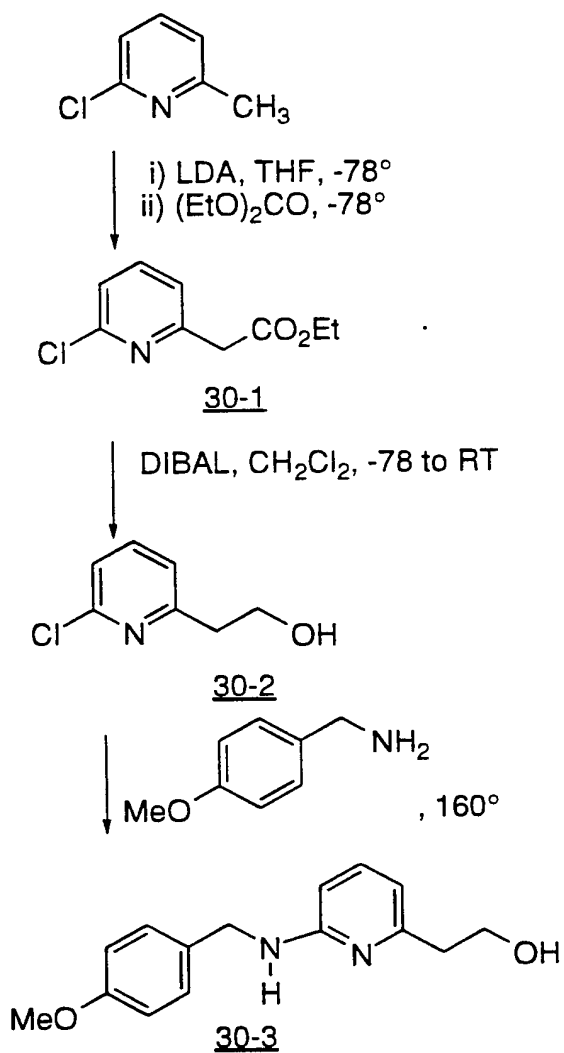
4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine (29-7)

Alkyne 29-6 (60 mg, 0.13 mmol), was suspended in 1.3 mL H₂O, 1 N NaOH was added until the mixture was homogeneous, 10%

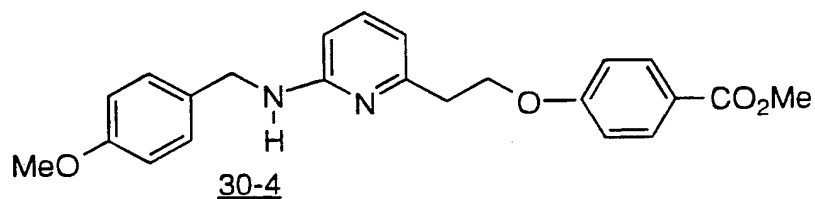
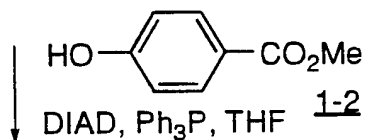
- 5 Pd/C (12 mg) was added, and an H₂ balloon was applied. After 16 h the reaction was filtered, concentrated, and purified by flash chromatography (silica, 12:10:1:1 EtOAc/EtOH/NH₄OH/H₂O) providing 29-7 as a white solid.

- 10 ¹H NMR (300 MHz, D₂O + NaOD) δ 7.73 (d, J=8 Hz, 2H), 7.52 (d, J=9 Hz, 2H), 7.34 (d, J=8 Hz, 2H), 7.30-7.15 (m, 3H), 6.67 (d, J=7 Hz, 1H), 6.62 (d, J=8 Hz, 1H), 3.80-3.68 (m, 2H), 3.35-3.05 (m, 5H).

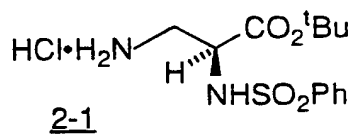
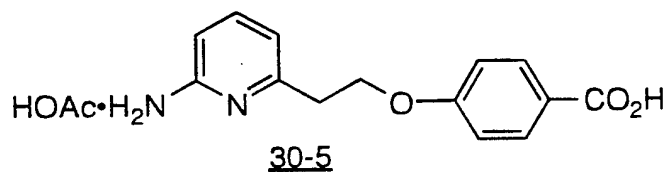
- 150 -

SCHEME 30

- 151 -

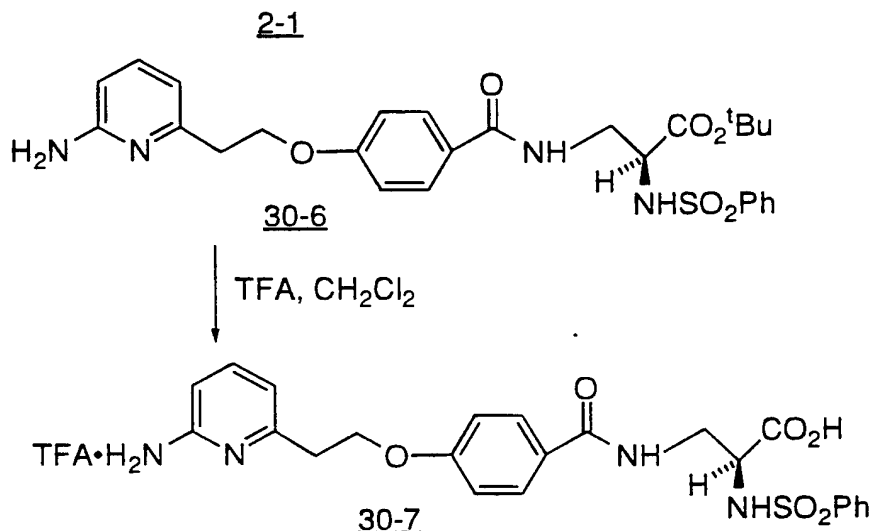
SCHEME 30 (CONT'D)30-3

↓ 6N HCl, 50°



EDC, HOBT, NMM, DMF

- 152 -

SCHEME 30 (CONT'D)Ethyl 2-Chloropyridin-6-ylacetate (30-1)

LDA (69 mmol) was prepared in 50 mL THF, cooled to
 5 -78°, and 6-chloro-2-picoline (Aldrich) (3.7 mL, 34 mmol) was added
 dropwise, forming a precipitate. After 15 min, diethylcarbonate (4.9
 mL, 41 mmol) was added, the burgundy solution was stirred at -78° for
 15 min more then quenched with sat. NH₄Cl. The mixture was warmed
 to RT, extracted twice with EtOAc, the organic layers were washed
 10 with brine, dried (MgSO₄), and concentrated. Flash chromatography
 (silica, 10% EtOAc/hexane) provided 30-1 as a yellow oil.

R_f 0.41 (silica, 20% EtOAc/hexane).

¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J=8 Hz, 1H), 7.27-7.24 (m, 2H),
 4.19 (q, J=7 Hz, 2H), 3.83 (s, 2H), 1.27 (t, J=7 Hz, 3H).

2-(2-Chloropyridin-6-yl)ethanol (30-2)

Ester 30-1 (1.34 g, 6.7 mmol) was dissolved in 10 mL
 CH₂Cl₂ at -78°, DIBAL (1 M in CH₂Cl₂, 17 mL, 17 mmol) was added,
 the mixture was warmed to RT for 15 min before quenching in a
 20 mixture of 25 mL saturated aqueous Na-K tartrate and 100 mL EtOAc.
 This mixture was shaken vigorously. The phases were allowed to
 separate, and the organic layer was washed with brine, dried (MgSO₄),

- 153 -

concentrated and chromatographed (silica, 40% EtOAc/hexane), providing 30-2 as a yellow oil.

R_f 0.26 (silica, 50% EtOAc/hexane).

¹H NMR (400 MHz, CDCl₃) δ 7.59 (t, J=8 Hz, 1H), 7.20 (t, J=8 Hz, 1H), 7.12 (d, J=8 Hz, 1H), 4.02 (q, J=6 Hz, 2H), 3.10 (t, J=6 Hz, 1H), 3.01 (t, J=5 Hz, 2H).

2-[2-(4-Methoxybenzylamino)pyridin-6-yl]ethanol (30-3)

Chloropyridine 30-2 (150 mg, 0.95 mmol) and 4-methoxybenzylamine (4 mL, 31 mmol) were combined neat and heated in a sealed tube at 160° for 4 days. After diluting with EtOAc and water the pH was adjusted to 7 phases separated and the organic phase was washed with brine, dried (MgSO₄) and concentrated. Flash chromatography (twice on silica, 50% and 40% EtOAc/hexane) provided 30-3 as a yellow semi-solid.

R_f 0.38 (silica, 50% EtOAc/hexane).

¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, J=8 Hz, 1H), 7.29-7.23 (m, 3H), 6.90-6.85 (m 3H), 6.43 (d, J=7Hz, 1H), 6.26 (d, J=8 Hz, 1H), 4.76 (br m, 1H), 4.39 (d, J=6 Hz, 2H), 3.95 (t, J=5 Hz, 2H), 3.80 (s, 3H), 2.84 (t, J=5 Hz, 2H).

Methyl 4-[2-(4-methoxybenzylamino)pyridin-6-yl]ethoxy]benzoate (30-4)

Methyl 4-hydroxybenzoate (68 mg, 0.45 mmol) and Ph₃P (175 mg, 0.67 mmol) were dissolved in 5 mL THF. A solution of 30-3 (115 mg, 0.44 mmol) and DIAD (123 μL, 0.62 mmol) in THF was slowly added. After 1 h the reaction was concentrated and purified by flash chromatography (silica, 20% EtOAc/hexane) providing 30-4 as an off-white solid.

R_f 0.64 (silica, 50% EtOAc/hexane).

¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, J=9 Hz, 2H), 7.36 (t, J=8 Hz, 1H), 7.28-7.24 (m, 2H), 6.93-6.83 (m, 4H), 6.55 (d, J= 7 Hz, 1H), 6.25 (d, J=8 Hz, 1H), 4.41-4.34 (m, 4H), 3.88 (s, 3H), 3.79 (s, 3H), 3.10 (t, J=7 Hz, 2H).

- 154 -

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoic acid acetate (30-5)

Ester 30-4 (240 mg, 0.61 mmol) was dissolved in 6N HCl and heated at 50° for 16 h. Concentration and flash chromatography (silica, 18:1:1 CH₂Cl₂/MeOH/HOAc) provided 30-5 as a light orange solid.

R_f 0.19 (silica, 18:1:1 CH₂Cl₂/MeOH/HOAc).

¹H NMR (300 MHz, DMSO) δ 7.88 (d, J=8 Hz, 2H), 7.29 (t, J=8 Hz, 1H), 6.90 (d, J=8 Hz, 2H), 6.45 (d, J=7 Hz, 1H), 6.29 (d, J=8 Hz, 1H), 4.30 (t, J=7 Hz, 2H), 2.94 (t, J=6 Hz, 2H), 1.83 (s).

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine t-butyl ester (30-6)

Acid 30-5 (100 mg, 0.31 mmol), amine 2-1 (210 mg, 0.59 mmol), EDC (90 mg, 0.47 mmol), HOBT (63 mg, 0.47 mmol) and NMM (150 μL, 1.4 mmol) were combined in 2 mL DMF at -15°. After warming to RT for 16 h the mixture was concentrated and chromatographed (silica, 9:1:1 CH₂Cl₂/MeOH/HOAc), providing 30-6. R_f 0.32 (silica, 9:1:1 CH₂Cl₂/MeOH/HOAc).

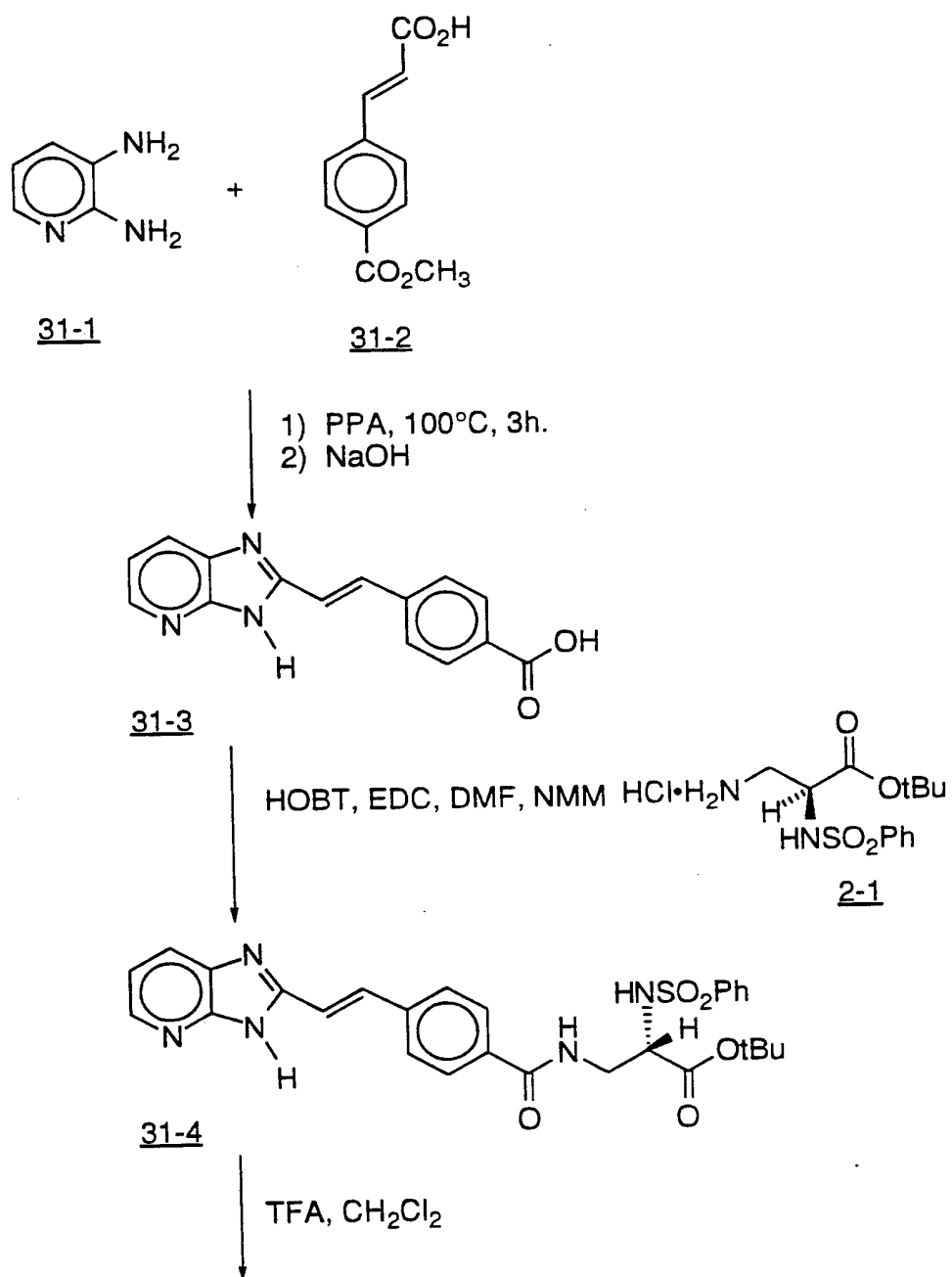
4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine (30-7)

Ester 30-6 (120 mg, 0.22 mmol) was dissolved in 1 mL CH₂Cl₂, and 1 mL TFA was added. After 1 h the reaction was concentrated azeotroped with toluene, chromatographed (silica, 18:1:1 → 9:1:1 → CH₂Cl₂/MeOH/HOAc) and purified by prep HPLC (C₁₈, 0.1% TFA in H₂O/CH₃CN) providing 30-7 as a white solid.

R_f 0.33 (silica, 4:1:1 CH₂Cl₂/MeOH/HOAc).

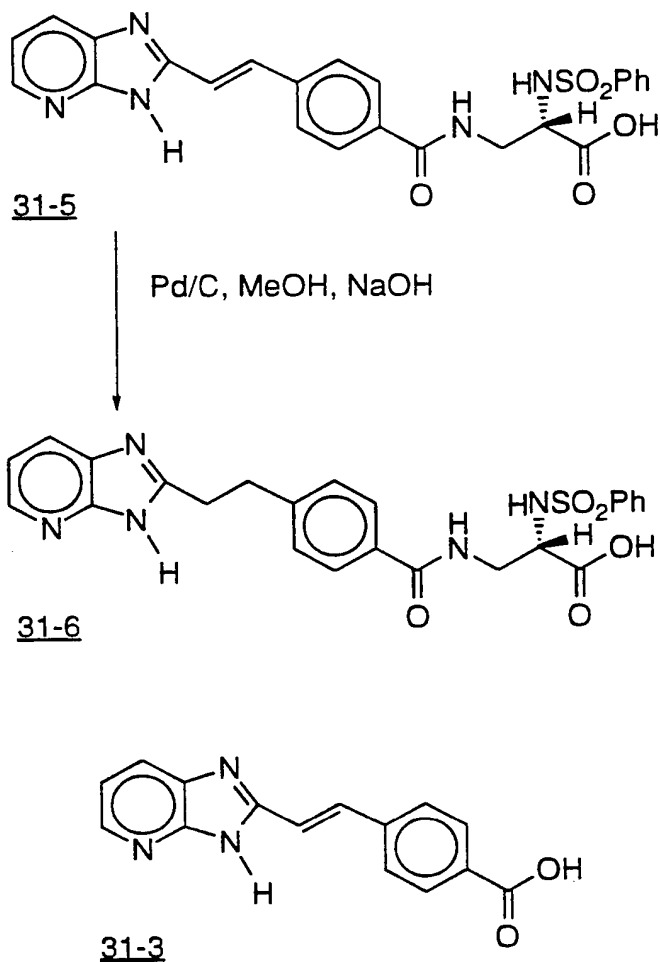
¹H NMR (400 MHz, D₂O) δ 7.46 (d, J=7 Hz, 2H), 7.36-7.29 (m, 3H), 7.02-6.95 (m, 3H), 6.79 (d, J=8 Hz, 2H), 6.57 (d, J=8 Hz, 1H), 6.39 (d, J=8 Hz, 1H), 4.28 (t, J=7 Hz, 2H), 3.50-3.40 (m, 2H), 2.98 (m, 1H), 2.91 (t, J=5 Hz, 2H).

- 155 -

SCHEME 31

- 156 -

SCHEME 31 (CONT'D)



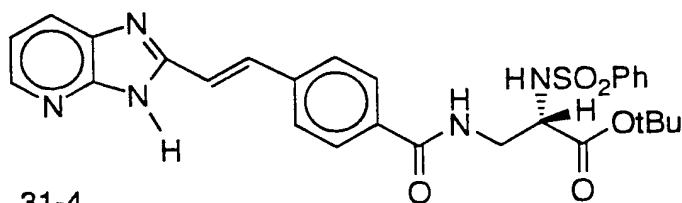
5

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoic acid (31-3)

A solution of 31-1 (546 mg, 5.0 mmol), (Aldrich) 3-2 (1030 mg, 5.0 mmol) (*Chem. Pharm. Bull.* 36(2), 495(1988)) and PPA (20 mL) was heated at 100°C for 3 h. After cooling, the reaction was poured into ice water and the yellow solid collected by filtration and added to 1N NaOH (50 mL). After stirring under ambient conditions for 18 h, the reaction was acidified with 12N HCl to provide 31-3 as a yellow solid.

- 157 -

^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 8.54 (m, 1H), 8.25 (m, 1H), 8.10 (d, $J=8\text{Hz}$, 2H), 8.02 (d, $J=16\text{Hz}$, 1H), 7.93 (d, $J=8\text{Hz}$, 2H), 7.46-7.54 (m, 2H).



5

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine t-butyl ester (31-4)

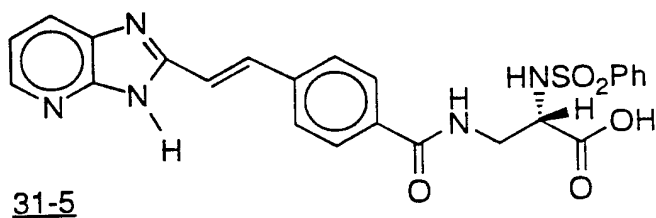
A DMF solution (10 mL) containing 31-3 (301 mg, 1.0 mmol) 2-1 (336 mg, 1.0 mmol), HOBT (206 mg, 1.35 mmol), EDC (258 mg, 1.35 mmol) and NMM (440 μl , 4.0 mmol) was stirred under ambient conditions for 18 h. The DMF was evaporated and the residue partitioned between CH_2Cl_2 and H_2O . The organic layer was dried (MgSO_4) and concentrated to a yellow gum which was purified by flash chromatography (silica, 4:1, $\text{CHCl}_3\cdot\text{NH}_3/\text{IPA}$) to provide impure 31-4 which was rechromatographed (silica, 9:1 EtOAc/IPA) to give 31-4 as a colorless foam.

15

R_f 0.33 (silica, 9:1 EtOAc/IPA).

^1H NMR (400 MHz, CD_3OD) δ 8.33 (dd, $J=5$, 1Hz, 1H), 7.95 (dd, $J=8$, 1Hz, 1H), 7.81-7.84 (m, 4H), 7.70-7.78 (m, 3H), 7.44-7.52 (m, 3H), 7.25-7.30 (m, 2H), 4.15 (dd, $J=8$, 6Hz, 1H), 3.69 (dd, $J=14$, 6Hz, 1H), 3.51 (dd, $J=8\text{Hz}$, 14Hz, 1H), 1.12 (s, 9H).

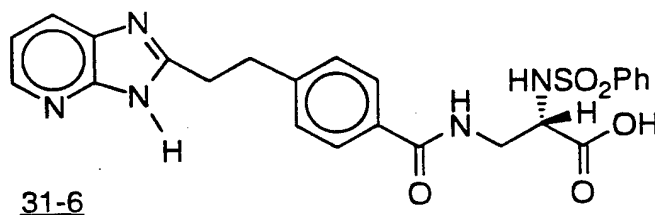
20



- 158 -

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine (31-5)

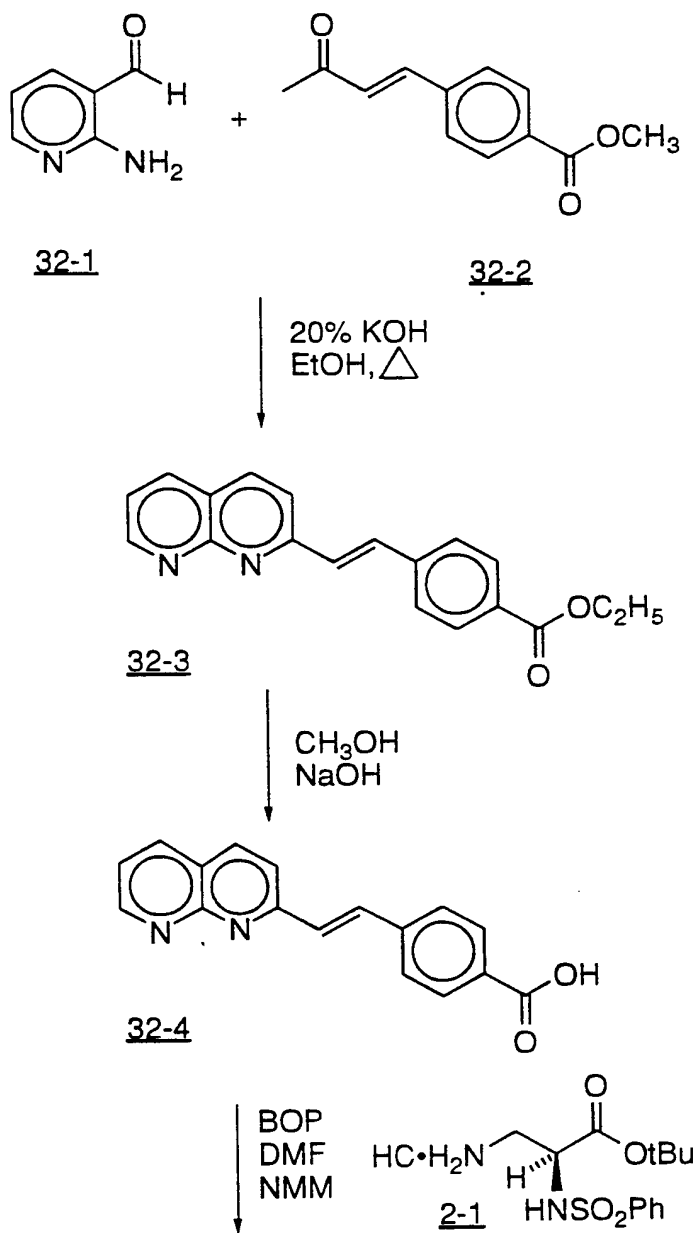
A CH₂Cl₂ solution (20 mL) of 31-4 (220 mg, 0.4 mmol) and TFA (5 mL) was stirred under ambient conditions for 5 h and concentrated. Flash chromatography (silica 9:0.5:0.5, EtOH/H₂O/NH₄OH) gave 31-5 as a solid.
¹H NMR (400 MHz, CD₃OD/NaOD) δ 8.08 (m, 1H), 7.81-7.87 (m, 5H), 7.68-7.75 (m, 3H), 7.33-7.37 (m, 4H), 6.98 (m, 1H), 3.65-3.72 (m, 2H), 3.32 (m, 1H).



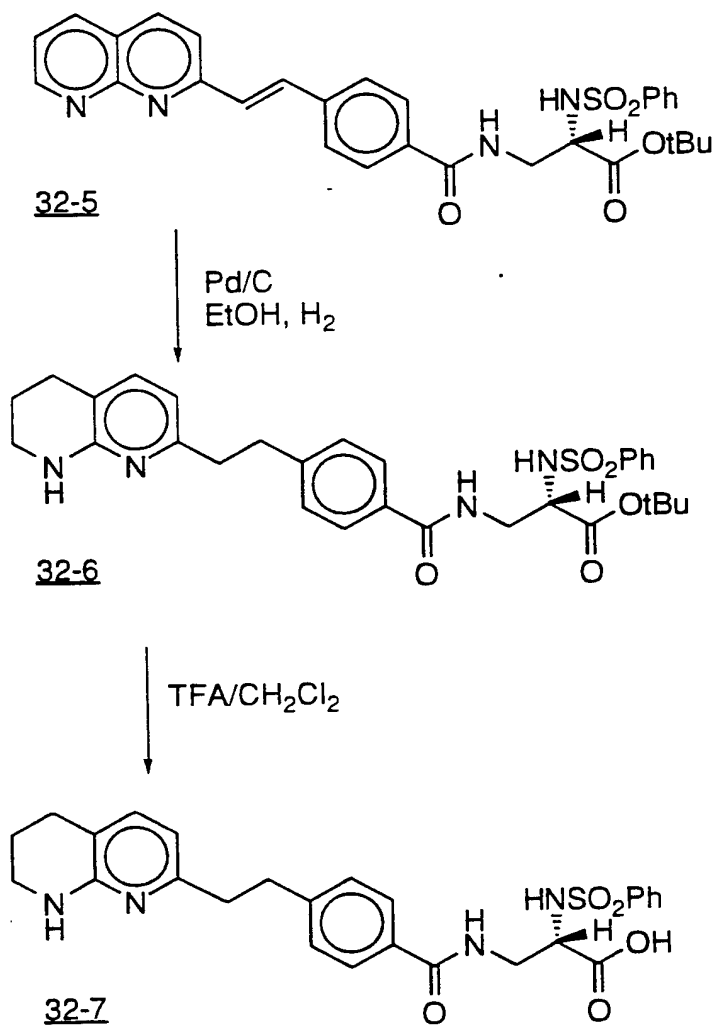
4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine (31-6)

A mixture of 31-5 (90 mg, 0.18 mmol), 10% Pd/C (50 mg), 1N NaOH (2 mL) and CH₃OH (20 mL) was hydrogenated at 1 atm for 18 h. After filtration and concentration the residue was neutralized with 10% HCl and the solid chromatographed (silica, 19:1 EtOH/NH₄OH) to provide 31-6 as a fluffy solid after trituration with aqueous TFA.
 R_f 0.48 (19:1 EtOH/NH₄OH).
¹H NMR (400 MHz, CD₃OD) δ 8.29 (dd, J=5, 1Hz, 1H), 7.91 (dd, J=8, 1Hz, 1H), 7.82 (m, 2H), 7.67 (d, J=8H, 2H), 7.38-7.48 (m, 3H), 7.30 (d, J=8, 1Hz, 2H), 7.25 (m, 1H), 3.87 (m, 1H), 3.65 (m, 1H), 3.53 (m, 1H), 3.26 (m, 2H).

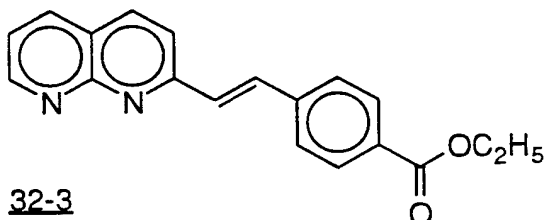
- 159 -

SCHEME 32

- 160 -

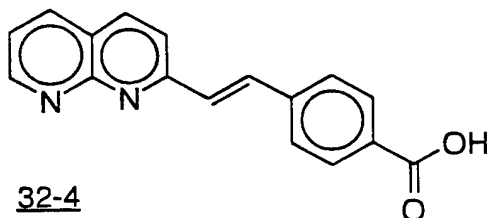
SCHEME 32 (CONT'D)

- 161 -



Ethyl 4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoate (32-3)

- An ethanol solution (10 mL) of 32-1 (260 mg, 2.1 mmol)
5 (*Syn. Comm.* 17(14), 1695(1987), 32-2 (435 mg, 2.1 mmol) (*Tet. Lett.* 34(4), 653(1993) and 20% KOH (100 ml) was refluxed for 6 hours. The reaction was concentrated to dryness and the residue partitioned between EtOAc and H₂O. The organic layer was washed with brine and dried (MgSO₄). Filtration and evaporation provided a yellow solid
10 which was purified by flash chromatography (silica, 4:1 EtOAc/hexane) to give 32-3 as a cream colored solid.
R_f 0.21 (silica, 3/1 EtOAc/hexane).
¹H NMR (300 MHz, CDCl₃) δ 9.12 (dd, J=4, 2Hz, 1H), 8.15-8.21 (m, 2H), 8.02-8.11 (m, 3H), 7.66-7.72 (m, 3H), 7.48 (d, J=16Hz, 1H), 7.45
15 (dd, J=8, 4Hz, 1H), 4.39 (q, J=7Hz, 2H), 1.41 (t, J=7Hz, 3H).



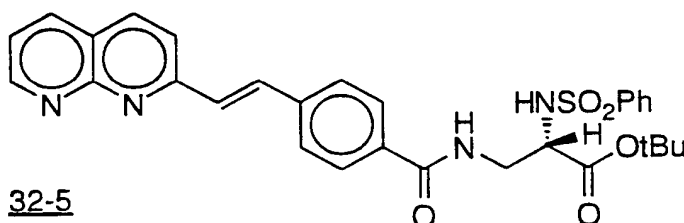
4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoic acid (32-4)

- A methanol solution (100 mL) of 32-3 (420 mg, 1.38
20 mmol) and 1N NaOH (13.8 mL, 13.8 mmol) was stirred at ambient conditions for 18 hrs and at reflux for 2 hrs. The reaction was concentrated to dryness and the residue dissolved in H₂O and the

- 162 -

solution acidified with 1M NaHSO₄ solution to give 32-4 as a pale yellow solid after filtration.

¹H NMR (300 MHz, CD₃OD) δ 9.05 (m, 1H), 8.43 (d, J=8Hz, 2H), 8.04-8.10 (m, 2H), 7.96-8.01 (m, 2H), 7.83 (d, J=8Hz, 2H), 7.61 (m, 2H).

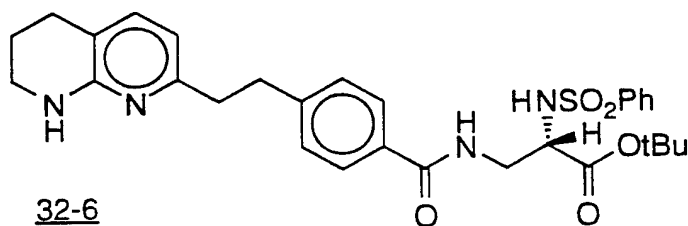


4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butylester (32-5)

To a stirred solution of 32-4 (396 mg, 1.38 mmol), 2-1 (556 mg, 1.65 mmol), NMM (728 μl, 6.62 mmol), and DMF (10 mL) was added BOP (732 mg, 1.65 mmol). After 18 h the reaction was concentrated to dryness and the residue partitioned between EtOAc and H₂O. The organic layer was washed with sat. NaHCO₃ solution, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 3:2 CH₂Cl₂/acetone) gave 32-5 as a yellow foam.

R_f 0.34 (silica, 3:2 CH₂Cl₂/acetone).

¹H NMR (300 MHz, CD₃OD) δ 9.05 (m, 1H), 8.41 (d, J=8Hz, 2H), 7.95-8.03 (m, 2H), 7.78-7.88 (m, 6H), 7.47-7.62 (m, 5H), 4.16 (m, 1H), 3.71 (m, 1H), 3.54 (m, 1H), 1.21 (s, 9H).



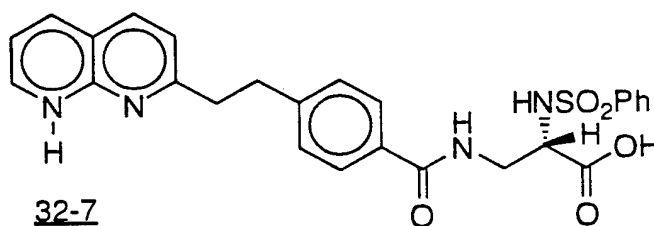
- 163 -

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester (32-6)

A mixture of 32-5 (670 mg, 1.2 mmol), 10% Pd/C (335 mg) and ethanol (50 mL) was stirred under a hydrogen atmosphere (1 atm) for 18 h. Filtration followed by concentration gave a yellow foam. Flash chromatography (silica, 97:3 CH₂Cl₂/CH₃OH gave 32-6 as a colorless foam.

R_f 0.26 (silica, 97:3 CH₂Cl₂/CH₃OH).

¹H NMR (300 MHz, CD₃OD) δ 7.82 (d, J=7Hz, 2H), 7.65 (d, J=8Hz, 2H), 7.42-7.54 (m, 3H), 7.25 (d, J=8Hz, 2H), 7.08 (d, J=7Hz, 1H), 6.29 (d, J=7Hz, 1H), 4.12 (dd, J=8, 6Hz, 1H), 3.66 (dd, J=12, 6Hz, 1H), 3.50 (dd, J=12, 8Hz, 1H), 3.37 (t, J=6Hz, 2H), 2.97 (t, J=6Hz, 2H), 2.81 (t, J=6Hz, 2H), 2.68 (t, J=6Hz, 2H), 1.86 (m, 2H), 1.23 (s, 9H).



15

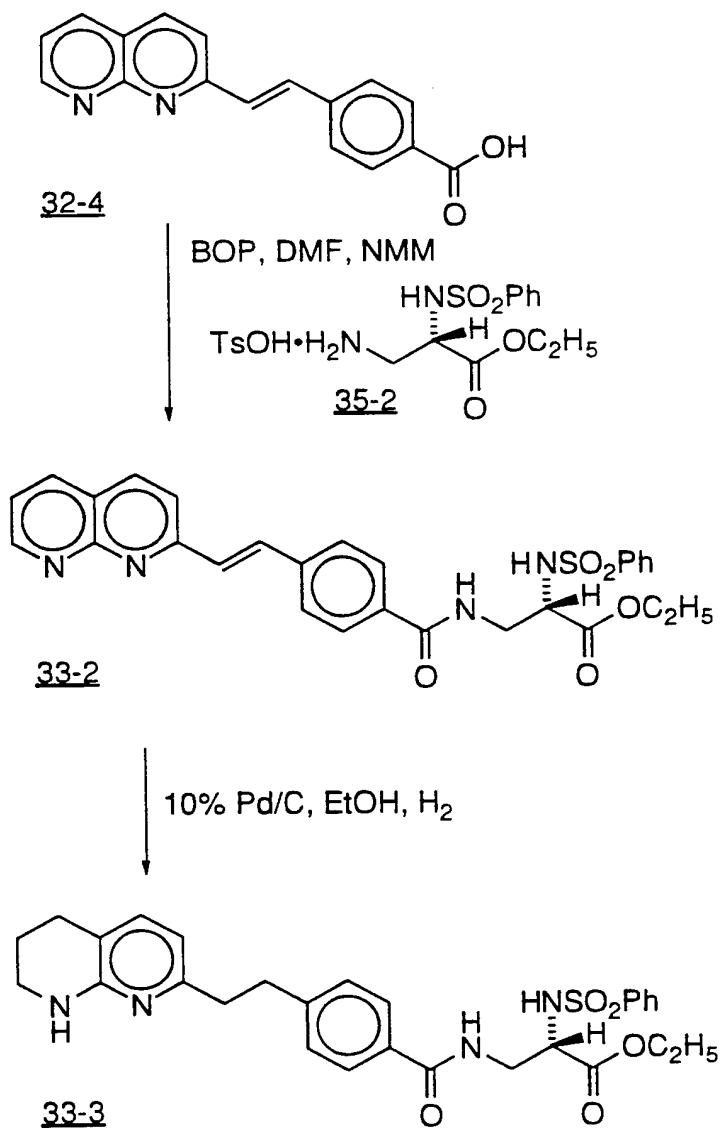
4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine (32-7)

A solution of 32-6 (221 mg, 0.39 mmol), TFA (5 mL) and CH₂Cl₂ (50 mL) was stirred under ambient conditions for 18 h. The reaction was concentrated and the solid residue purified by flash chromatography (silica, 19:1 EtOH/NH₄OH) to give 32-7 as a pale yellow solid.

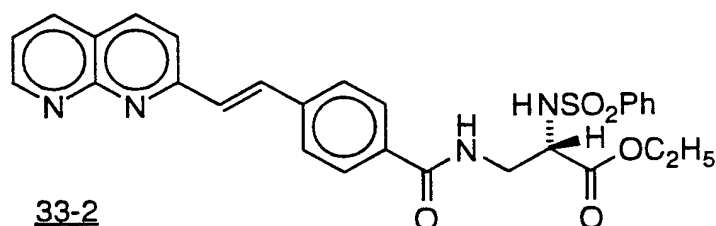
R_f 0.63 (silica, 19:1 EtOH/NH₄OH).

¹H NMR (300 MHz, CD₃OD) δ 7.82 (d, J=7Hz, 2H), 7.69 (d, J=8Hz, 2H), 7.28-7.34 (m, 3H), 7.25 (d, J=8Hz, 2H), 7.08 (d, J=7Hz, 1H), 6.29 (d, J=7Hz, 1H), 3.78 (m, 1H), 3.58-3.70 (m, 2H), 3.38 (t, J=6Hz, 2H), 2.97 (t, J=6Hz, 2H), 2.81 (t, J=6Hz, 2H), 2.68 (t, J=6Hz, 2H), 1.86 (m, 2H).

- 164 -

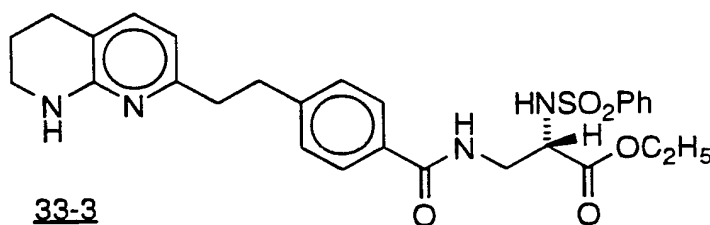
SCHEME 33

- 165 -



4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonyl-
amino- β -alanine ethyl ester (33-2)

- Following the procedure for coupling 32-4 to 2-1, 32-4
 5 (2.2 g, 7.96 mmol) was coupled to 35-2 (4.24 g, 9.55 mmol). Flash
 chromatography (silica, 3:2 Acetone/CH₂Cl₂) gave 33-2 as a pale
 yellow foam.
 R_f 0.31 (silica, 1:1 acetone/CH₂Cl₂).
¹H NMR (300 MHz, CD₃OD) δ 9.05 (m, 1H), 8.41 (d, J=8Hz, 2H),
 10 7.95-8.04 (m, 2H), 7.77-7.86 (m, 6H), 7.55-7.64 (m, 5H), 4.24 (m, 1H),
 3.91 (q, J=7Hz, 2H), 3.70 (m, 2H), 3.57 (m, 2H), 1.06 (t, J=7Hz, 3H).



- 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-
 15 2(S)-phenylsulfonylamino- β -alanine ethyl ester (33-3)

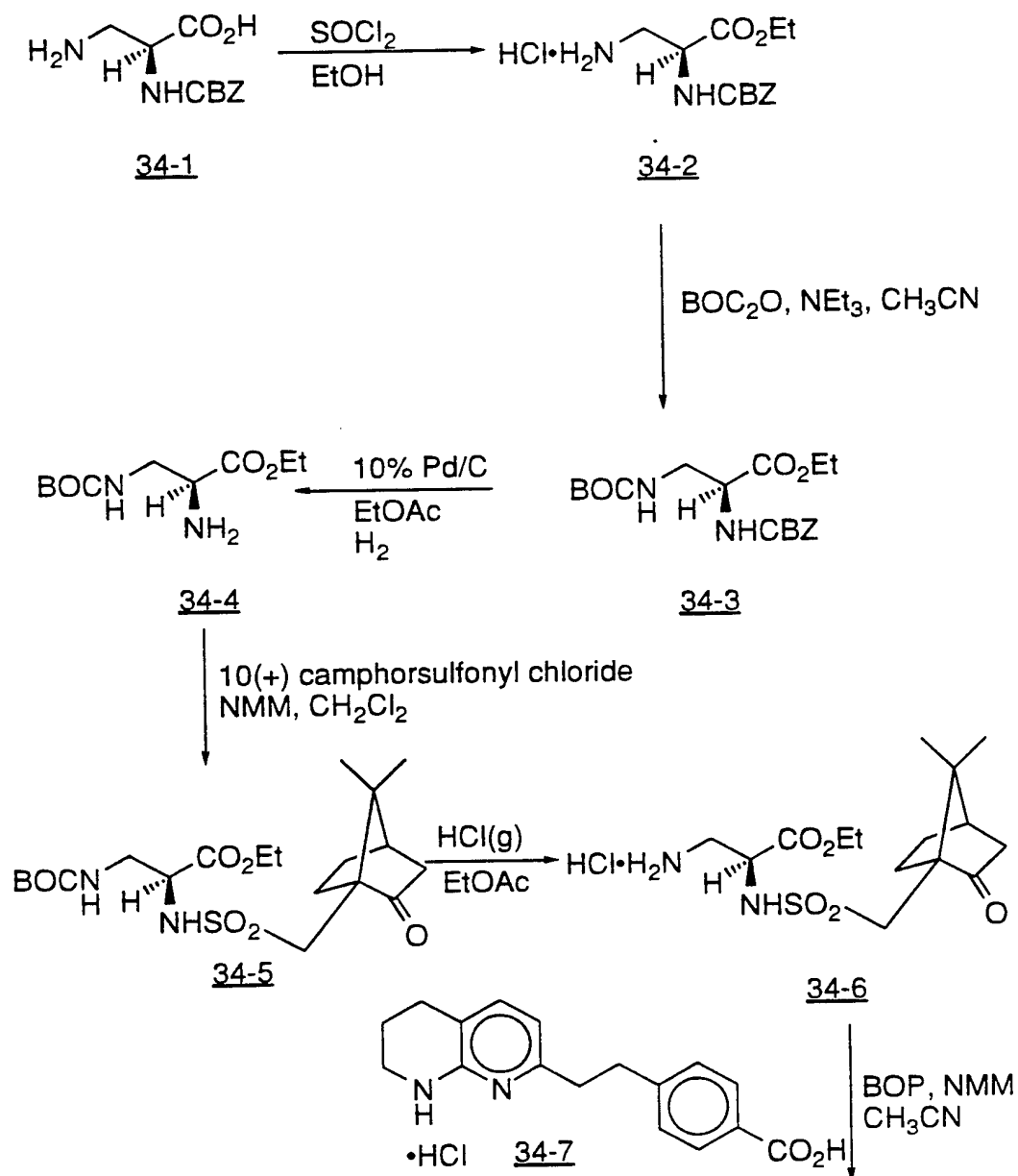
- A mixture of 33-2 (1.3 g, 2.45 mmol), 10% Pd/C (650 mg)
 and ethanol (100 ml) was stirred under a hydrogen atmosphere (1 atm)
 for 18 hr. Filtration followed by concentration gave a yellow foam
 which was purified by flash chromatography (silica, 49:1
 20 EtOAc/EtOH•NH₃) to provide 33-3 as a pale yellow solid.
 R_f 0.42 (silica, 49:1 EtOAc/NH₃ saturated EtOH•NH₃).
¹H NMR (300 MHz, CD₃OD) δ 7.81 (d, J=7Hz, 2H), 7.64 (d, J=8Hz,
 2H), 7.40-7.56 (m, 3H), 7.25 (d, J=8Hz, 2H), 7.14 (d, J=7Hz, 1H), 6.33
 (d, J=7Hz, 1H), 4.19 (t, J=6Hz, 1H), 3.89 (q, J=7Hz, 2H), 3.63 (m, 1H),

- 166 -

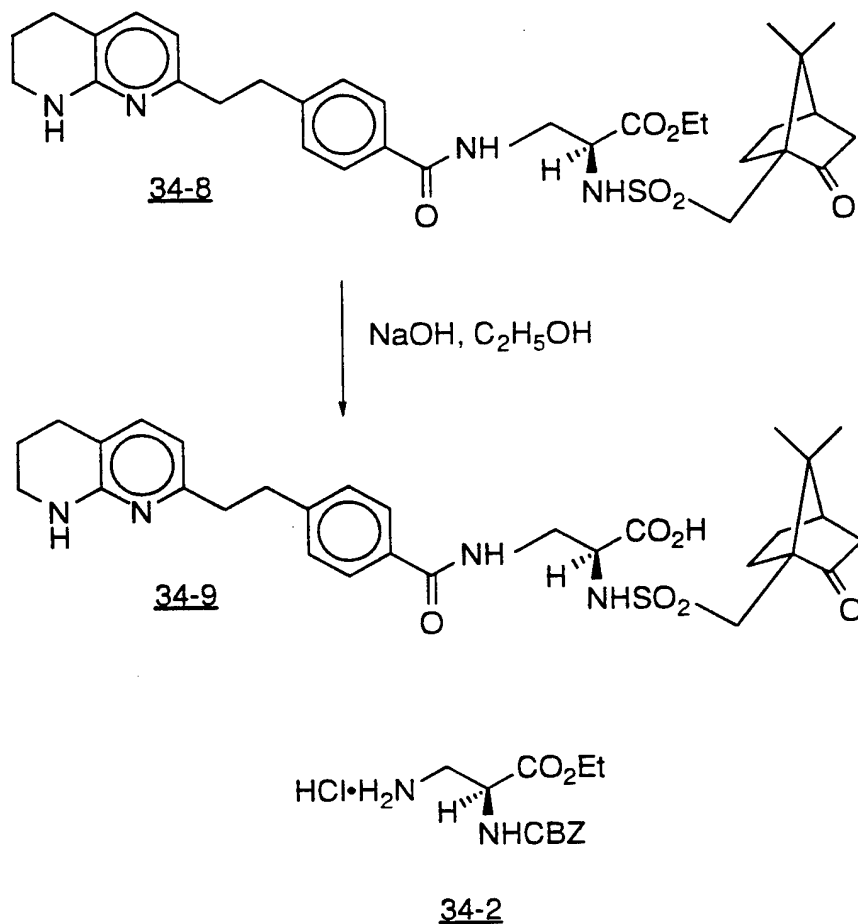
3.53 (m, 1H), 3.39 (t, J=6Hz, 2H), 2.99 (t, J=8Hz), 2.83 (t, J=8Hz, 2H), 2.69 (t, J=6Hz, 2H), 1.87 (m, 2H), 1.04 (t, J=7Hz, 3H).

SCHEME 34

5



- 167 -

SCHEME 34 (CONT'D)

5

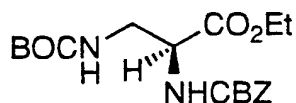
Ethyl 2(S)-N α -Cbz-2,3-diaminopropionate hydrochloride (34-2)

34-1 (5 g, 21 mmol) was dissolved in 100 mL EtOH and cooled to 0°C. SOCl₂ (9.2 mL, 126 mmol) was added followed by removal of the cooling bath. After 6 hours, the reaction was concentrated to provide **34-2** as a white solid.

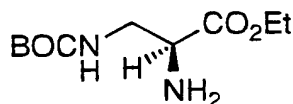
¹H NMR (300 MHz, CD₃OD) δ 7.35 (m, 5H), 5.14 (s, 2H), 4.44 (m, 1H), 4.22 (q, J=7Hz, 2H), 3.43 (m, 1H), 3.20 (m, 1H), 1.25 (t, J=7Hz, 3H).

15

- 168 -

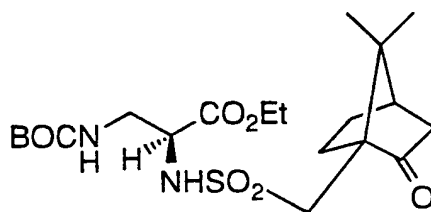
34-3Ethyl 2(S)-N α -Cbz-N β -Boc-2,3-diaminopropionate (34-3)

- 34-2 (2 g, 6.6 mmol) was dissolved in 60 mL CH₃CN. NEt₃ (1 mL, 7.2 mmol) was added followed by BOC₂O (1.58 g, 7.3 mmol). After two hours, the reaction was concentrated, diluted with EtOAc, washed with sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄), filtered and concentrated to provide 34-3 as a clear oil. TLC R_f 0.87 (silica, 80% EtOAc/hex). ¹H NMR (300 MHz, CDCl₃) δ 7.35 (s, 5H), 5.75 (bs, 1H), 5.12 (s, 2H), 4.81 (bs, 1H), 4.39 (m, 1H), 4.19 (m, 2H), 3.56 (m, 2H), 1.42 (s, 9H), 1.29 (q, J=7Hz, 3H).

34-4Ethyl 2(S)-N β -Boc-2,3-diaminopropionate (34-4)

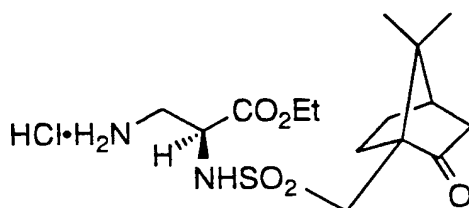
- 34-3 (2.4 g, 6.6 mmol) with 10% Pd/C (240 mg) in EtOAc (35 mL) was stirred under a H₂ atmosphere for 20 hours. The reaction was filtered through a celite pad and concentrated to provide 34-4 as a clear oil. TLC R_f 0.13 (silica, 80% EtOAc/hex). ¹H NMR (300 MHz, CDCl₃) δ 5.00 (bs, 1H), 4.19 (m, 2H), 3.55 (m, 2H), 3.25 (m, 1H), 1.44 (s, 9H), 1.29 (q, J=7Hz, 3H).

- 169 -

34-5

Ethyl-2(S)-N α -(1(S)10-camphorsulfonylamino-N β -Boc-2,3-diaminopropionate (34-5)

- Amine 34-4 (760 mg, 3.27 mmol) was dissolved in 35 mL CH₂Cl₂ and cooled to 0°C. NMM (755 μ L, 6.87 mmol) and 10(+) camphorsulfonyl chloride (1.23 g, 4.9 mmol) were added. After stirring at 0°C for one hour, the reaction was concentrated, then diluted with EtOAc, washed with H₂O, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄), and concentrated to an oil. Flash chromatography (silica, 25-40% EtOAc/hexanes) provided 34-5 as a clear oil. TLC R_f 0.66 (silica, 50% EtOAc/hexanes). ¹H-NMR (300 MHz, CDCl₃) δ 6.37 (d, J=8Hz, 1H), 4.99 (bt, 1H), 4.32 (m, 1H), 4.23 (q, J=8Hz, 2H), 3.56 (m, 3H), 3.0 (d, J=15 Hz, 1H), 2.4 (m, 1H), 2.05 (m, 4H), 1.43 (s, 9H), 1.30 (t, J=7 Hz, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

34-6

Ethyl-2(S)-N α -(1(S)10-camphorsulfonylamino)-2,3-diaminopropionate hydrochloride (34-6)

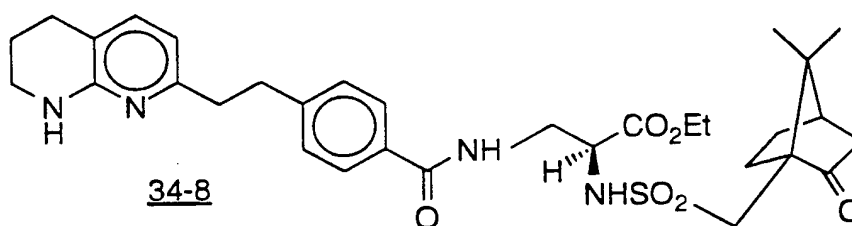
- Ester 34-5 (900 mg, 2.18 mmol) was dissolved in 15 mL EtOAc and cooled to 0°C. HCl (g) was bubbled through the reaction mixture for 15 minutes. The reaction was removed from the cooling

- 170 -

bath and purged with Ar (g) for 20 minutes followed by concentration to provide 34-6 as a foamy solid.

TLC R_f 0.05 (silica, 20% MeOH/EtOAc).

¹H-NMR (300 MHz, CDCl₃): δ 4.75 (m, 1H), 4.26 (q, J=7Hz, 2H), 3.50 (m, 4H), 2.40 (m, 3H), 1.98 (m, 4H), 1.30 (t, J=7Hz, 3H), 1.04 (s, 3H), 0.91 (s, 3H).

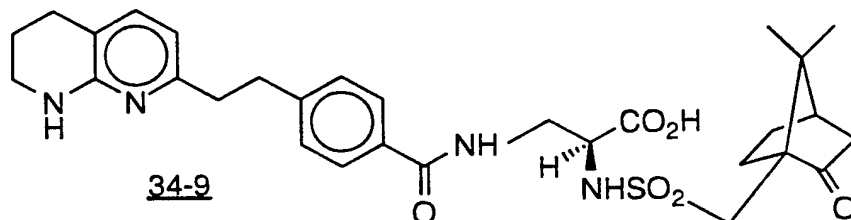


4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-
 10 2(S)[1(S)10-camphorsulfonylaminol] β-alanine ethyl ester (34-8)
34-7 (Scheme 37) (200 mg, 0.627 mmol), amine 34-6 (240 mg, 0.69 mmol), NMM (345 μL, 3.13 mmol) and BOP reagent (332 mg, 0.75 mmol) were combined in 5 mL CH₃CN. After stirring overnight, the reaction was concentrated, then diluted with EtOAc, washed with H₂O, sat. NaHCO₃ and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, EtOAc) provided 34-8 as an off-white foamy solid.

TLC R_f 0.13 (silica, EtOAc).

¹H NMR (300 MHz, CDCl₃) δ 7.70 (d, J=8Hz, 2H), 7.25 (d, J=8Hz, 2H), 7.03 (d, J=7Hz, 1H), 6.72 (t, J=5Hz, 1H), 6.5 (bm, 1H), 6.28 (d, J=7Hz, 1H), 4.79 (s, 1H), 4.42 (bs, 1H), 4.25 (q, J=7Hz, 2H), 4.04 (m, 1H), 3.85 (m, 1H), 3.55 (d, J=15Hz, 1H), 3.41 (m, 2H), 3.00 (m, 3H), 2.82 (t, J=4Hz, 2H), 2.69 (t, J=6Hz, 2H), 2.04 (m, 8H), 1.58 (bs, 3H), 1.31 (t, J=7Hz, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

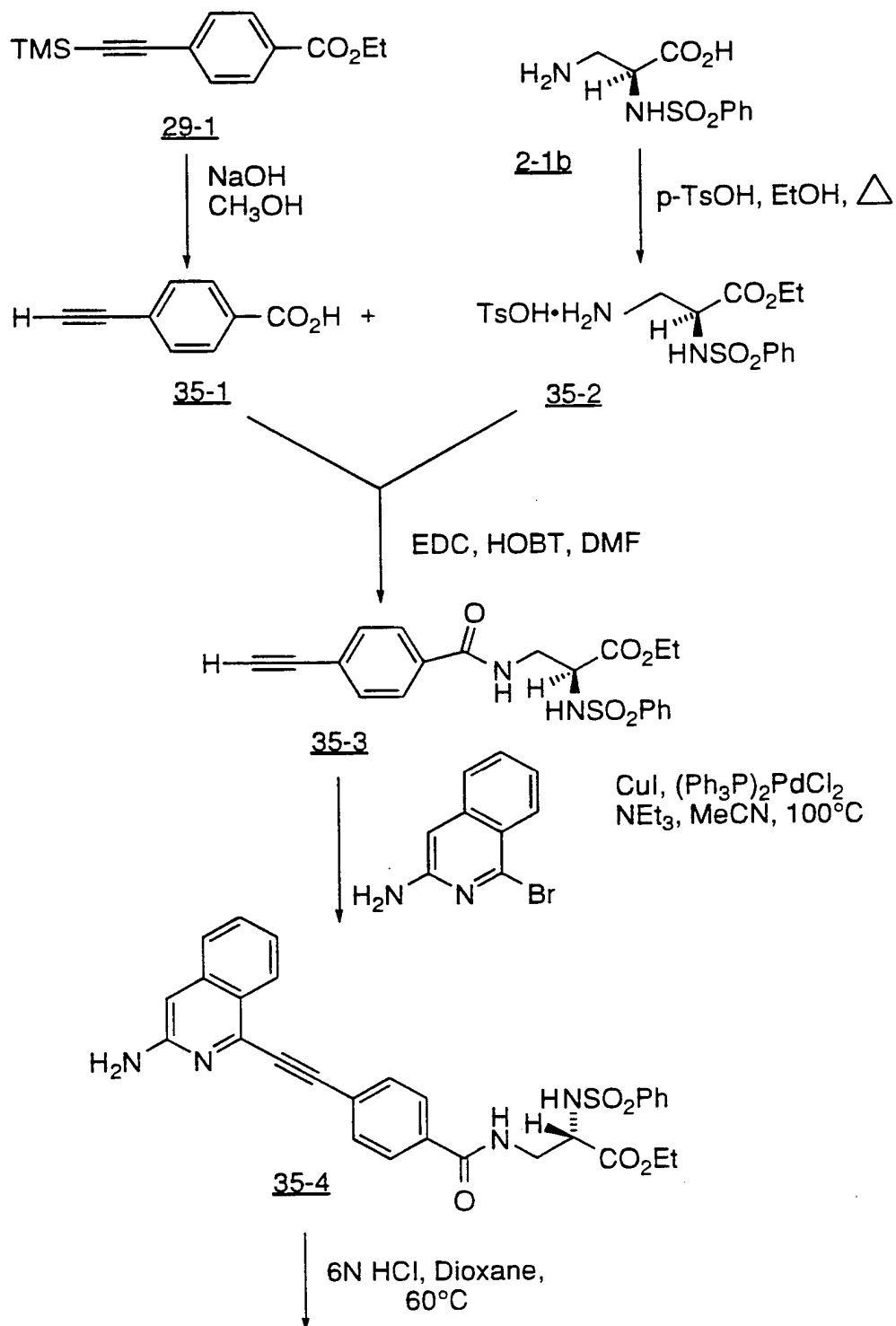
- 171 -



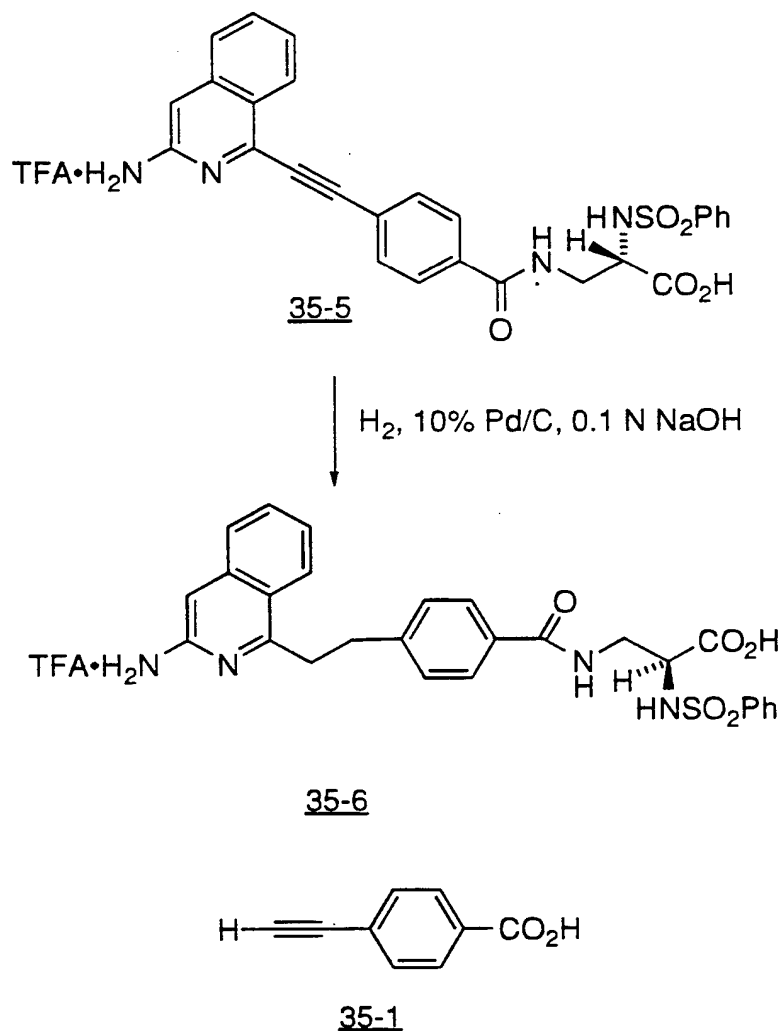
4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-
2(S)-[1(S)10-camphorsulfonylamino] β -alanine (34-9)

- 34-8 (250 mg, 0.409 mmol) was dissolved in 4 mL EtOH,
5 1M NaOH (1.02 mL, 1.02 mmol) was added and the reaction mixture
was stirred for two hours. The reaction mixture was neutralized with
1N HCl and then concentrated to a foamy solid. Flash chromatography
(silica, 18:10:1:1 EtOAc/EtOH/NH₄OH/H₂O) provided 34-9 as a
slightly yellow solid.
- 10 TLC R_f 0.49 (silica, 12:10:1:1 EtOAc/EtOH/NH₄OH/H₂O).
¹H NMR (400 MHz, DMSO) δ 8.48 (bt, 1H), 7.72 (d, J=8Hz, 2H), 7.55
(bs, 1H), 7.28 (d, J=8Hz, 2H), 7.02 (d, J=7Hz, 1H), 6.37 (s, 1H), 6.26
(d, J=7Hz, 1H), 4.13 (s, 1H), 3.54 (m, 3H), 3.37 (m, 2H), 2.94 (m, 3H),
2.73 (t, J=7Hz, 2H), 2.6 (t, J=6Hz, 2H), 2.3 (m, 3H), 2.02 (m, 1H), 1.89
15 (m, 2H), 1.75 (m, 2H), 1.49 (m, 1H), 1.37 (m, 1H), 1.05 (m, 1H), 0.95
(s, 3H), 0.66 (s, 3H).

- 172 -

SCHEME 35

- 173 -

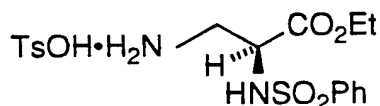
SCHEME 35 (CONT'D)5 4-Ethynylbenzoic acid (35-1)

A solution of ethyl ester 29-1 (9.06 g, 36.8 mmol) and aqueous 1N NaOH solution (92 mL, 92 mmol) in MeOH (300 mL) was stirred overnight. The mixture was concentrated. The residue was dissolved in water then acidified with 6N HCl before extracting twice
 10 with EtOAc. The organic layers were combined and washed with 5% KHSO₄ solution and brine, then dried (MgSO₄) and concentrated to give 1-1 as a brown solid.

- 174 -

TLC R_f 0.38 (silica, 10% iPrOH/EtOAc).

¹H NMR (300 MHz, d₆-DMSO) δ 7.93 (d, J=9Hz, 2H), 7.60 (d, J=9Hz, 2H), 4.46 (s, 1H).



5

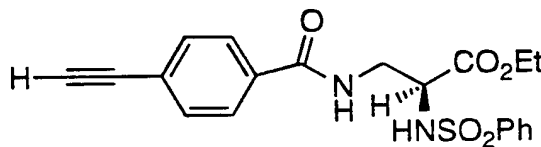
35-2

Ethyl 2(S)-phenylsulfonylamino-β-alanine p-toluenesulfonate (35-2)

Acid 2-1b (13.20 g, 54.1 mmol) was suspended in 500 mL EtOH, p-TsOH-H₂O (11.3 g, 59 mmol) was added and the mixture was heated at reflux overnight. After distilling off the solvent, fresh EtOH
10 was added and distilled off, then more EtOH was added and the mixture was distilled to 100 mL at which point 800 mL ether was added. After cooling to 4°, solvent was decanted from the gum which was rinsed with additional ether, and dried, providing 35-2 as a hygroscopic glass.

Additional 35-2 was recovered from the solvent phase by concentration and triturating with ether (2x).
15

¹H NMR (400 MHz, D₂O) δ 7.91 (d, J=8Hz, 2H), 7.75 (t, J=8Hz, 1H), 7.70 (d, J=8Hz, 2H), 7.65 (t, J=8Hz, 2H), 7.37 (d, J=8Hz, 2H), 4.42 (dd, J=10, 4Hz, 1H), 3.86 (t, J=7Hz, 2H), 3.50 (dd, J=13.5Hz, 1H), 3.20 (dd, J=13, 10Hz, 1h), 2.40 (s, 3H), 0.99 (t, J=7Hz, 3H).
20

35-3

4-Ethynylbenzoyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester (35-3)

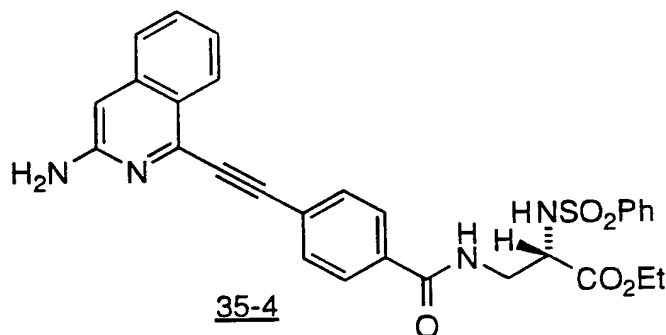
4-Ethynylbenzoic acid (35-1) (3.10 g, 21.2 mmol), 35-2
25 (8.58 g, 19.3 mmol), NMM (8.49 mL, 7.72 mmol), HOBT (3.39 g, 25.1 mmol), and EDC (4.81 g, 25.1 mmol) were combined in 96 mL DMF

- 175 -

and stirred overnight. The reaction was concentrated, residue was diluted with EtOAc and washed with water (2x) and brine, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (silica, 45-50% EtOAc/Hexane) gave 35-3 as a white solid.

5 TLC R_f 0.27 (silica, 45% EtOAc/Hexane).

¹H-NMR (300 MHz, d₆-DMSO) δ 8.63 (t, J=6Hz, 1H), 8.47 (br s, 1H), 7.75 (m, 4H), 7.52 (m, 5H), 4.39 (s, 1H), 4.11 (t, J=7Hz, 1H), 3.78 (q, J=7Hz, 2H), 3.44 (m, 3H), 0.94 (t, J=7Hz, 3H).



10 4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine ethyl ester (35-4)

Ethyl ester 35-3 (0.50 g, 1.25 mmol), 3-amino-1-bromoisquinoline (0.279 g, 1.25 mmol), triethylamine (0.697 mL, 5.00 mmol), CuI (10 mg, 0.053 mmol), and (Ph₃P)₂PdCl₂ (20 mg, 0.028 mmol) were combined in 5 mL acetonitrile in a sealed pressure tube under Ar and heated to 100°C overnight. The dark solution was cooled and diluted with EtOAc, then washed with water (2x) and brine, dried (MgSO₄), filtered, and concentrated. Flash chromatography

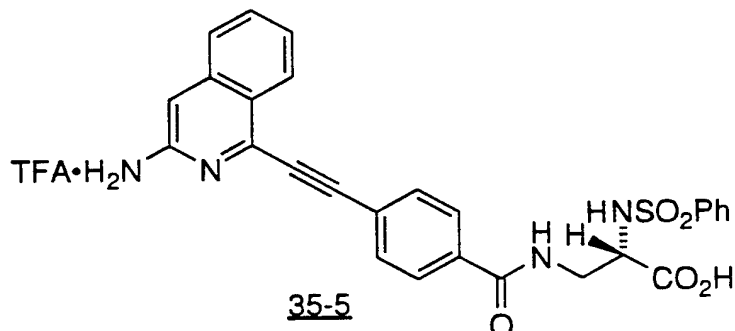
20 (silica, 75% EtOAc/Hexane) gave 35-4 as a greenish foam.

TLC R_f 0.21 (silica, 75% EtOAc/Hexane).

¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, J=8Hz, 1H), 7.88 (d, J=9Hz, 2H), 7.82 (d, J=8Hz, 2H), 7.77 (d, J=8Hz, 2H), 7.55 (m, 5H), 7.35 (tm, J=7Hz, 1H), 7.27 (s, 1H), 6.80 (s, 2H), 5.80 (br s, 1H), 4.56 (s, 2H),

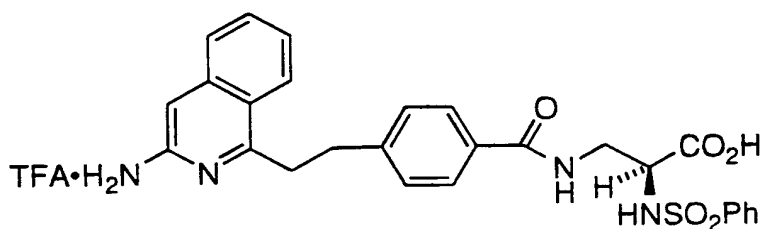
25 4.11 (m, 3H), 3.97 (m, 1H), 3.68 (m, 1H), 1.17 (t, J=7Hz, 3H).

- 176 -



4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonyl-amino- β -alanine trifluoroacetate (35-5)

- A solution of ester 35-4 (0.46 g, 0.85 mmol) in dioxane (4 mL) and 6N HCl (8.5 mL) was heated to 60°C overnight. Concentration yielded an orange solid. Prep. HPLC (C₁₈, 0.1% TFA H₂O/CH₃CN) followed by lyophilization gave trifluoroacetate 35-5 as an orange solid.
- TLC R_f 0.25 (silica, 33:20:1:1 EtOAc:EtOH:NH₄OH:H₂O).
- ¹H NMR (400 MHz, CD₃OD) δ 8.27 (dm, J=9Hz, 1H), 7.87 (m, 6H), 7.68 (m, 2H), 7.50 (m, 4H), 7.15 (s, 1H), 4.24 (dd, J=9, 5Hz, 1H), 3.79 (m, 1H), 3.51 (m, 1H).

35-6

- 4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonyl-amino- β -alanine trifluoroacetate (35-6)

A mixture of acetylene 35-5 (0.085 g, 0.13 mmol) and 10% palladium on carbon (40 mg) in aqueous 0.1 N NaOH was stirred under a hydrogen balloon overnight. The suspension was filtered through

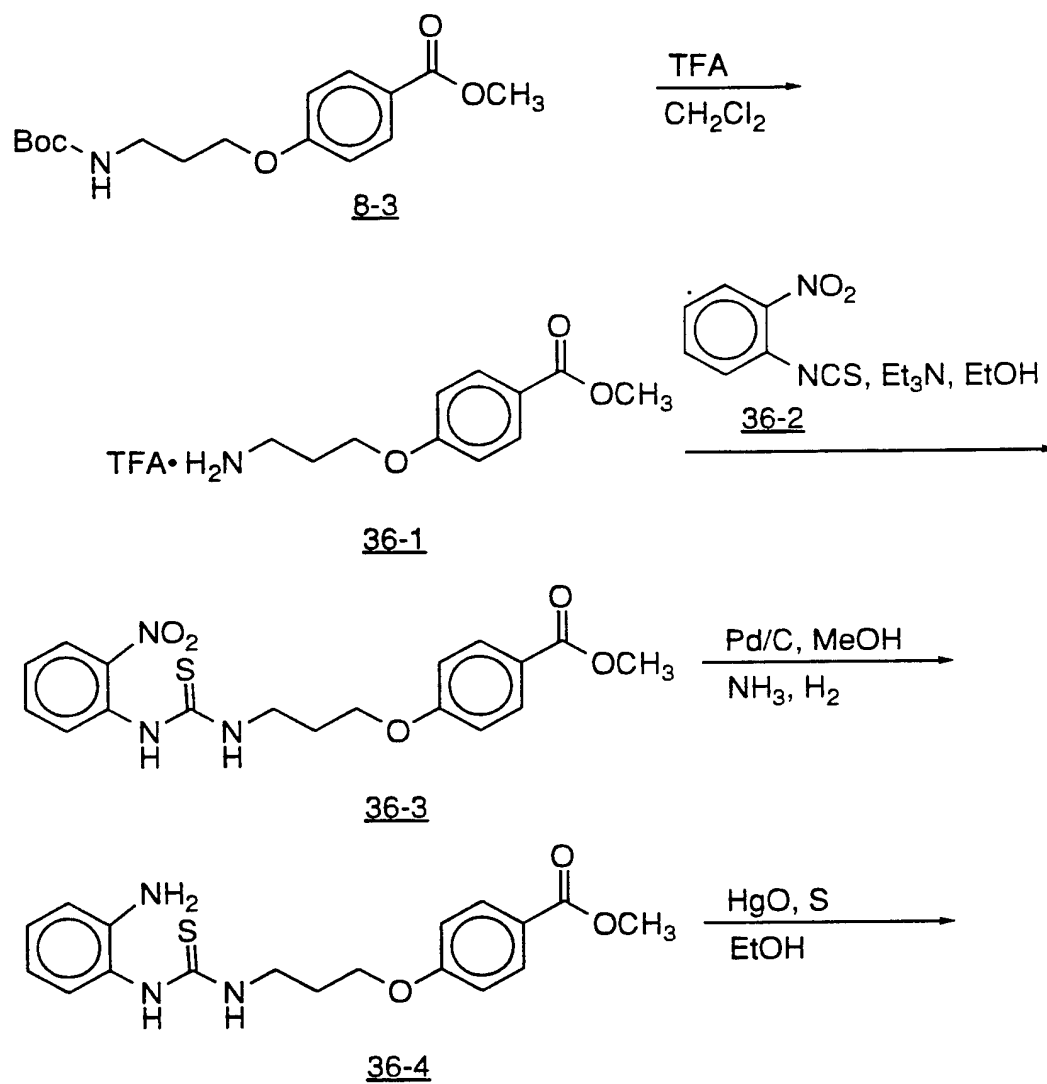
- 177 -

celite and concentrated to a dark oil. Prep. HPLC (C₁₈, 0.1% TFA H₂O/CH₃CN) followed by lyophilization gave 35-6 as a fluffy, yellow solid.

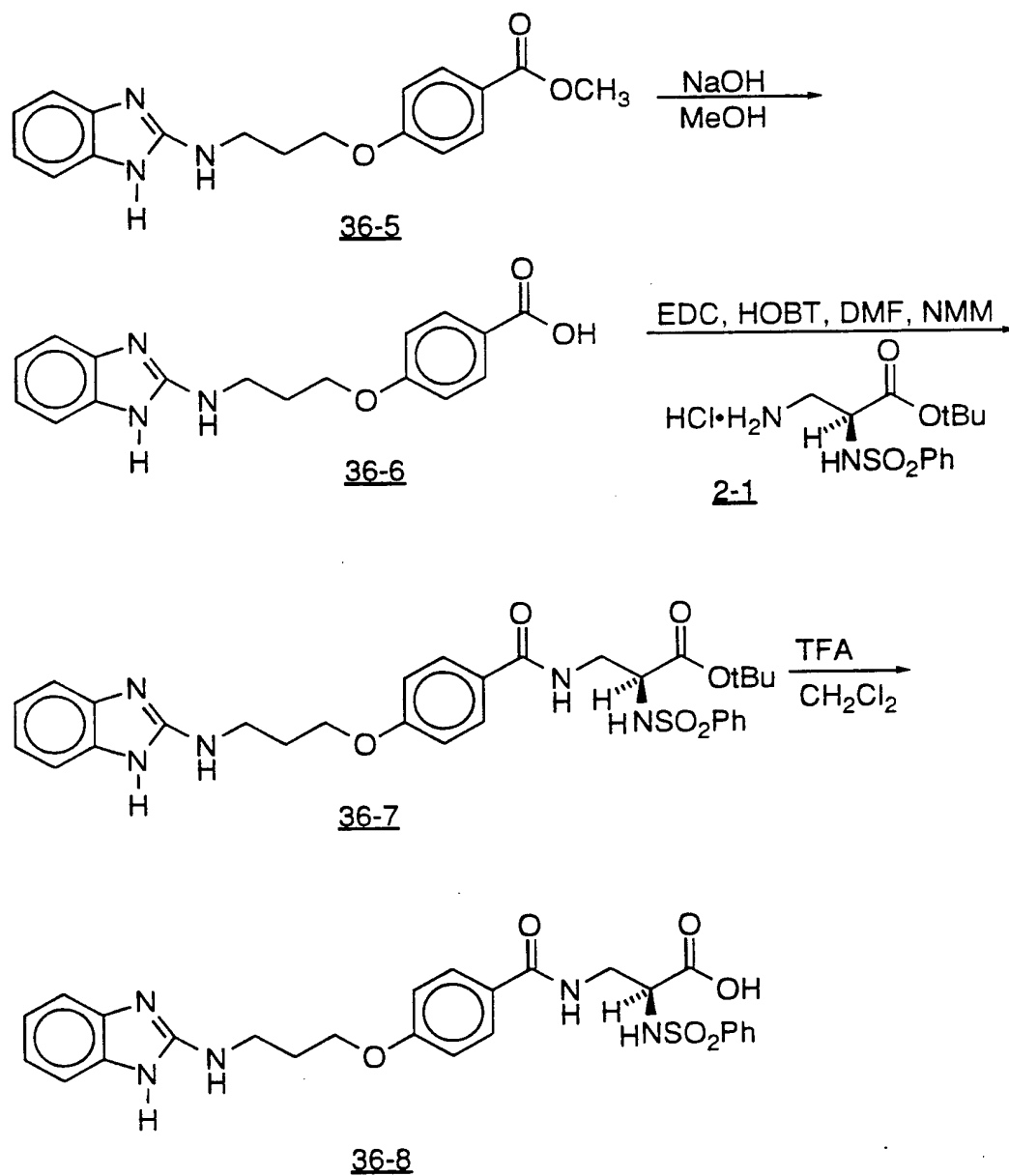
TLC R_f 0.51 (silica, 22:1:1 iPrOH/NH₄OH/H₂O).

- 5 ¹H NMR (400 MHz, d₆-DMSO) δ 8.40 (t, J=6Hz, 1H), 8.22 (d, J=9Hz, 1H), 8.14 (d, J=9Hz, 1H), 7.75 (d, J=7Hz, 2H), 7.68 (m, 3H), 7.60 (m, 1H), 7.52 (m, 1H), 7.45 (m, 2H), 7.38 (d, J=8Hz, 2H), 7.28 (t, J=7Hz, 1H), 6.86 (br, s, 1H), 4.04 (m, 1H), 3.35 (m), 3.11 (t, J=8Hz, 2H).

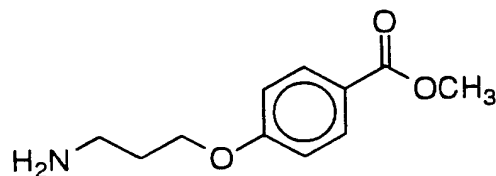
- 178 -

SCHEME 36

- 179 -

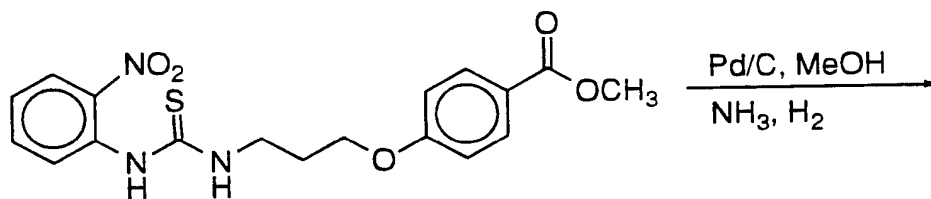
SCHEME 36 (CONT'D)

- 180 -

36-14-(3-aminopropoxy)benzoic acid methyl ester trifluoroacetate (36-1)

A CH₂Cl₂ solution (25 mL) of 8-3 (2.8 g, 8.97 mmol) and TFA (5 mL) was stirred under ambient conditions for 2 hr. The reaction was concentrated and the residue azeotroped with toluene to give a sticky solid which was triturated with hexane/ether (1:1) to provide 36-1 as a solid.

¹H NMR (400 MHz, CD₃OD) δ 7.97 (d, J=8Hz, 2H), 7.02 (d, J=8Hz, 2H), 4.19 (t, J=7Hz, 2H), 3.86 (s, 3H), 3.16 (t, J=7Hz, 2H), 2.17 (m, 2H).

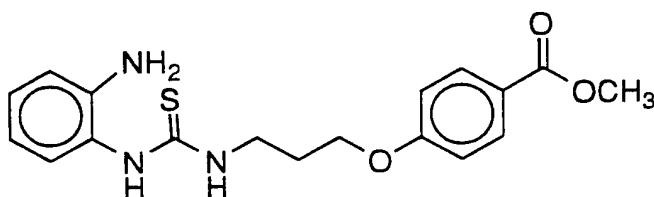
36-34-[3-[3-(2-nitrophenyl)thioureido]propoxy]benzoic acid methyl ester (36-3)

An ethanol solution (20 mL) of 36-1 (2.65 g, 8.19 mmol), 36-2 (1.47 g, 8.19 mmol) (Lancaster), and Et₃N (2.28 mL, 16.4 mmol) was stirred under ambient conditions for 18 h. The reaction was concentrated and the residue purified by flash chromatography (silica, 19:1 CH₂Cl₂/acetone) to provide 36-3 as a yellow foam.

R_f 0.23 (silica, 19:1 CH₂Cl₂/acetone).

¹H NMR (400 MHz, CDCl₃) δ 8.14 (dd, J=8, 2Hz, 1H), 7.96 (d, J=8Hz, 2H), 7.58 (m, 1H), 7.23 (m, 1H), 6.81-6.87 (m, 3H), 4.17 (t, J=7Hz, 2H), 3.89 (m, 5H), 2.22 (m, 2H).

- 181 -

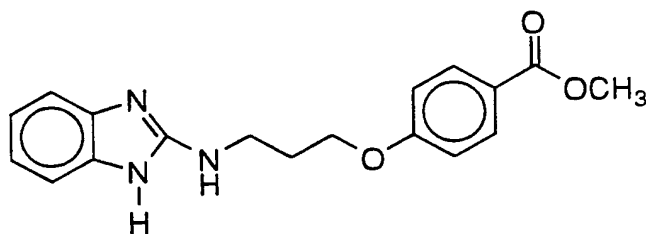
36-4

4-[3-[3-(2-aminophenyl)thioureido]propoxy]benzoic acid methyl ester
(36-4)

- 5 A methanol solution (150 mL) of 36-3 (3.15 g, 8.08 mmol) was saturated with NH₃. 10% Pd/C (2 g) was added and the mixture hydrogenated at 1 atm for 4 h. Filtration and concentration provided 36-4 as a purple solid.

R_f 0.18 (silica, 19:1 CH₂Cl₂/acetone).

- 10 ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, J=8Hz, 2H), 7.17 (m, 1H), 7.07 (m, 1H), 6.72-6.79 (m, 2H), 6.62 (d, J=8Hz, 2H), 4.05 (t, J=7Hz, 2H), 3.83-3.89 (m, 5H), 2.11 (m, 2H).

36-5

- 15 4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoic acid methyl ester (36-5)

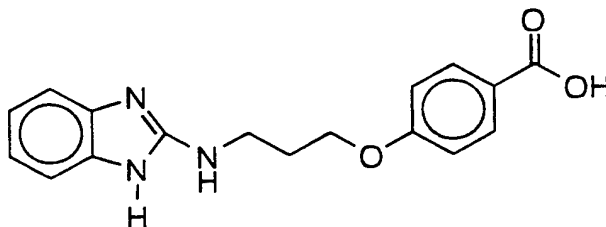
A mixture of 36-4 (2.5 g, 7.0 mmol), HgO (3.0 g, 13.9 mmol), sulfur (42 mg) and EtOH (50 mL) was refluxed for 2.5 h.

- 20 Filtration and concentration gave a brown gum which was purified by flash chromatography (silica, 9:1 CH₂Cl₂/CH₃OH) to provide 36-5 as a tan solid.

R_f 0.29 (silica, 9:1 CH₂Cl₂/CH₃OH).

- 182 -

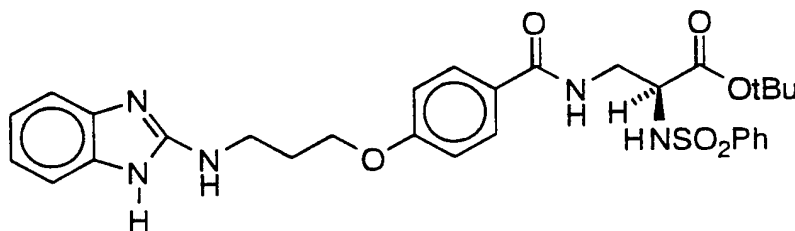
^1H NMR (400 MHz, CD_3OD) δ 7.94 (d, $J=9\text{Hz}$, 2H), 7.18 (m, 2H), 7.00 (d, $J=9\text{Hz}$, 2H), 6.96 (m, 2H), 4.19 (t, $J=6\text{Hz}$, 2H), 3.86 (s, 3H), 3.58 (t, $J=6\text{Hz}$, 2H), 2.16 (m, 2H).

36-6

4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoic acid (36-6)

A methanol solution (50 mL) of 4-5 (1.3 g, 4.0 mmol) and 1N NaOH (20 mL, 20 mmol) was stirred at 50°C for 4 h. The reaction was concentrated and the residue acidified with 1M NaHSO_4 solution to provide 4-6 as a beige colored solid.

^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, $J=9\text{Hz}$, 2H), 7.32 (m, 2H), 7.20 (m, 2H), 6.95 (t, $J=9\text{Hz}$, 2H), 4.21 (t, $J=6\text{Hz}$, 2H), 3.62 (t, $J=6\text{Hz}$, 2H), 2.22 (m, 2H).

36-7

4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-2(S)-phenylsulfonylamino-beta-alanine t-butyl ester (36-7)

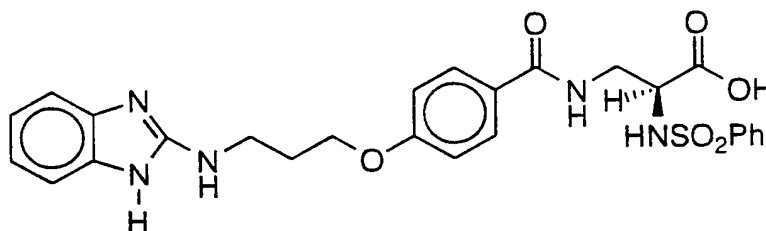
A DMF solution (10 mL) of 36-6 (311 mg, 1.0 mmol), 2-1 (370 mg, 1.1 mmol), HOBT (168 mg, 1.1 mmol), NMM (330 μl , 3.0 mmol) and EDC (211 mg, 1.1 mmol) was stirred under ambient

- 183 -

conditions for 18 h. Concentration and flash chromatography (silica, 85:15 EtOAc/CH₃OH) gave 36-7 as a pale yellow foam.

R_f 0.20 (silica, 85:15 EtOAc/CH₃OH).

¹H NMR (400 MHz, CD₃OD) δ 7.83 (d, J=8Hz, 2H), 7.73 (d, J=9Hz, 2H), 7.46-7.54 (m, 3H), 7.26-7.30 (m, 2H), 7.10-7.13 (m, 2H), 6.98 (d, J=9Hz, 2H), 4.20 (m, 2H), 3.63 (m, 3H), 3.44 (m, 1H), 3.31 (m, 1H), 2.19 (m, 2H), 1.23 (s, 9H).

36-8

10

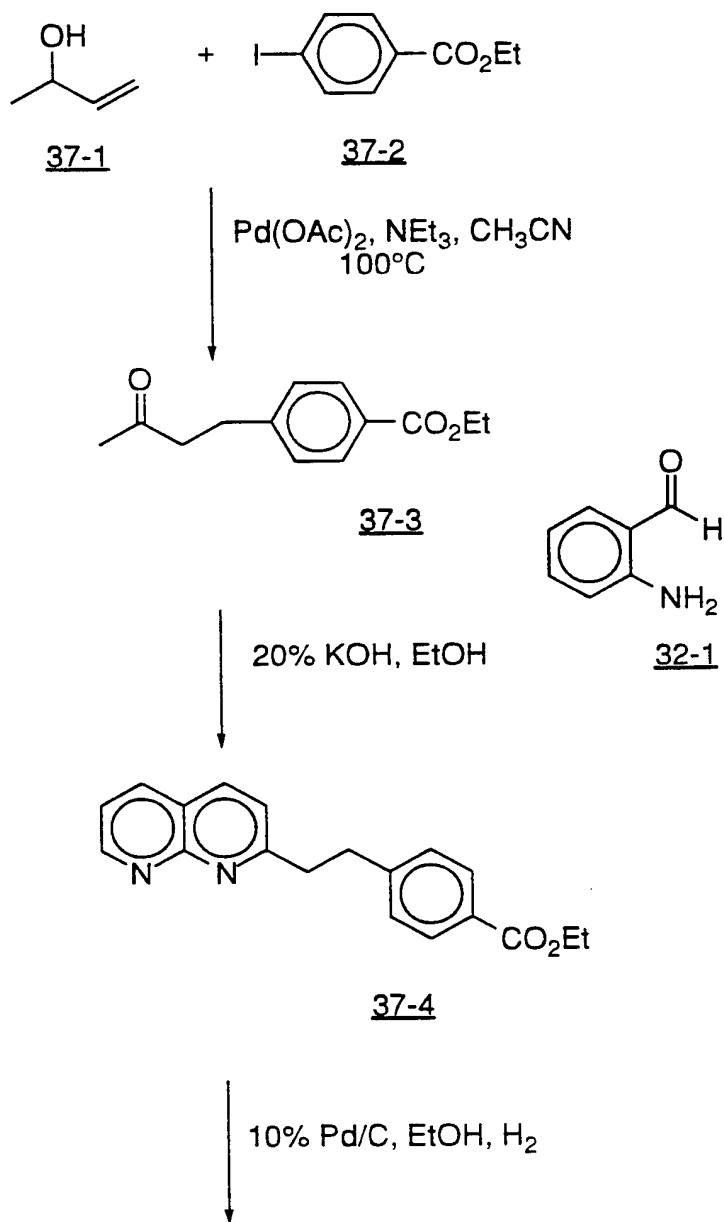
4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-2(S)-
phenylsulfonylamino-β-alanine (36-8)

A CH₂Cl₂ solution (20 mL) of 36-7 (580 mg, 0.97 mmol) and TFA (5 mL) was stirred under ambient conditions for 2 h and at 50°C for 2 h. Concentration and flash chromatography (silica, 9:0.5:0.5 EtOH/H₂O/NH₄OH) gave 36-8 as a pale yellow solid.

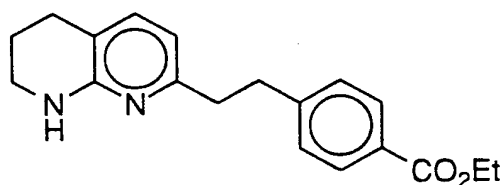
R_f 0.29 (silica 9.8:0:1:0.1 EtOH/H₂O/NH₄OH).

¹H NMR (400 MHz, CD₃OD) δ 7.83 (m, 2H), 7.76 (d, J=9Hz, 2H), 7.32-7.34 (m, 3H), 7.17-7.19 (m, 2H), 6.99 (d, J=9Hz, 2H), 6.85-6.88 (m, 2H), 4.20 (t, J=6Hz, 2H), 3.58-3.65 (m, 4H), 3.36 (m, H), 2.16 (m, 2H).

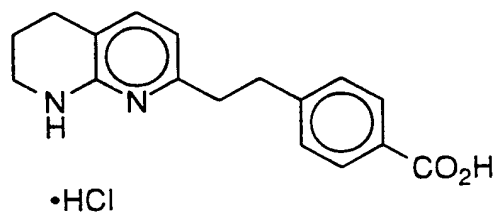
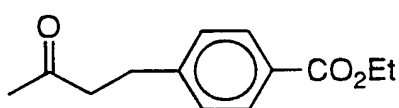
- 184 -

SCHEME 37

- 185 -

SCHEME 37 (CONT'D)37-5

6N HCl, 50°C

34-737-3

5

Ethyl-4-(2-butanone)benzoate (37-3)

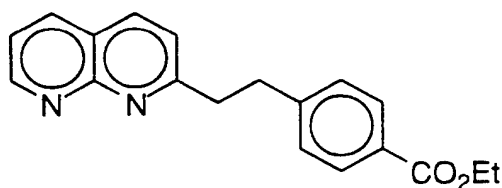
3-Buten-2-ol 37-1 (2.15 mL, 25 mmol), ethyl 4-iodobenzoate 37-2 (5.52 g, 20 mmol) and NEt₃ (3.5 mL, 25 mmol) were combined in 6 mL of CH₃CN under Ar in a pressure tube. Pd(OAc)₂ (19 mg, 0.08 mmol) was added and the reaction heated to 100°C for 3 hours. The reaction was cooled, then diluted with Et₂O, washed with H₂O, 10% KHSO₄, sat. NaHCO₃ and brine, dried

- 186 -

(MgSO₄) and concentrated to a yellow oil. Flash chromatography (silica, 10% EtOAc/hex) provided 37-3 as a clear oil.

TLC R_f 0.23 (silica, 30% EtOAc/hex).

¹H NMR (300 MHz, CDCl₃): δ 7.95 (d, J=8Hz, 2H), 7.25 (d, J=8Hz, 2H), 4.36 (q, J=7Hz, 2H), 2.95 (t, J=7Hz, 2H), 2.78 (t, J=7Hz, 2H), 2.15 (s, 2H), 1.38 (t, J=7Hz, 3H).

37-4

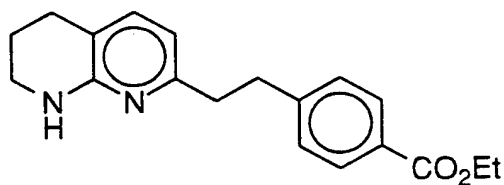
10 Ethyl 4-[2-(1,8-naphthyridin-7-yl)ethyl]benzoate (37-4)

An ethanol solution of (70 mL) of 37-3 (3.15 g, 14.3 mmol), 32-1 (1.75 g, 14.3 mmol) and 20% KOH (2 mL) was refluxed for 18 hours. The reaction was concentrated to dryness and the residue partitioned between EtOAc and H₂O. The organic layer was washed with sat. NaHCO₃ and brine, dried (MgSO₄) and concentrated to give a yellow oil. Flash chromatography (silica, 60%-80% EtOAc/hex) provided 37-4 as a yellow solid.

TLC R_f 0.31 (silica, 70% EtOAc/hex).

¹H NMR (300 MHz, CDCl₃) δ 9.11 (m, 1H), 8.18 (d, J=8Hz, 1H), 8.08 (d, J=8Hz, 1H), 7.95 (d, J=8Hz, 2H), 7.47 (m, 1H), 7.30 (d, J=8Hz, 2H), 4.35 (q, J=7Hz, 2H), 3.35 (m, 4H), 1.38 (t, J=7Hz, 3H).

- 187 -

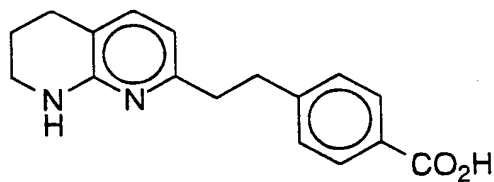
37-5

Ethyl 4-[2-(1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoate
(37-5)

5 A mixture of 37-4 (645 mg, 2.11 mmol), 10% Pd/C (65 mg), and ethanol (10 mL) was stirred under a hydrogen atmosphere for 18 hr. Filtration through a celite pad followed by concentration provided by 37-5 as an off white solid.

TLC R_f 0.75 (silica, 70% EtOAc/hex).

10 ¹H NMR (300 MHz, CDCl₃) δ 7.94 (d, J=8Hz, 2H), 7.26 (d, J=8Hz, 2H), 7.03 (d, J=7Hz, 1H), 6.28 (d, J=7Hz, 1H), 4.81 (s, 1H), 4.35 (q, J=7Hz, 2H), 3.40 (m, 2H), 3.03 (m, 2H), 2.84 (m, 2H), 2.69 (t, J=6Hz, 2H), 1.93 (t, J=6Hz, 2H), 1.38 (t, J=7Hz, 3H).



•HCl

34-7

15

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoic acid
hydrochloride (34-7)

20 Ester 37-5 (680 mg, 2.11 mmol) in 10 mL 6N HCl was heated to 50°C for 18 hours. Concentration provided 34-7 as a yellow solid.

- 188 -

¹H NMR (300 MHz, CD₃OD) δ 7.93 (d, J=8Hz, 2H), 7.52 (d, J=8Hz, 1H), 7.31 (d, J=8Hz, 2H), 6.54 (d, J=8Hz, 1H), 3.48 (t, J=5Hz, 2H), 3.03 (m, 4H), 2.79 (t, J=6Hz, 2H), 1.93 (t, J=6Hz, 2H).

- 5 The test procedures employed to measure the bone resorption inhibiting activity of the compounds of the present invention are described below.

BONE RESORPTION-PIT ASSAY

- 10 When osteoclasts engage in bone resorption, they will literally cause the formation of pits in the surface of bone that they are acting upon. Therefore, when testing compounds for their ability to inhibit osteoclasts, it is useful to measure the ability of osteoclasts to excavate these resorption pits when the inhibiting compound is present.

- 15 Consecutive cross sections (4.4 x 4.4 x 0.2 mm) of bovine femur were cut from the diaphysis with a low-speed diamond saw (Isomet, Beuhler, Ltd., Lake Bluff, IL.) by the method of Arnett and Dempster. *Endocrinology*, 120: 602-608.

- 20 Prior to incubation with osteoclasts, slices were rehydrated in 0.1 ml complete medium 199 in a 48-well plate (Costar, Cambridge, MA) overnight in the presence of twice the desired dose of compound being tested.

- 25 Osteoclasts were isolated from the long bones of 1 to 3-day-old rats (Sprague-Dawley) by adaptations of methods used by Chambers, *et al.*, *J. Cell Sci.*, 66: 383-399.

- 30 Femora, tibiae, and humeri were split and minced with scalpel blades into 2-5 ml Medium 199 (GIBCO, New York). The resulting suspension was gently pipetted (60 times with a wide-bore pipet and then aliquoted onto petri dished (Costar) or bone slices (0.1 ml per slice). Cells were allowed to settle for 30-40 minutes at 37°C. in moist CO₂-air before gently washing and reincubation in undiluted incubation medium. Osteoclast yields varied from 300 to 1400 per rat and typically comprised 1% or less of the total cell population.

- 189 -

Osteoclasts were counted at the day of isolation and after 1 day of incubation by phase-contrast microscopy (Nikon Diaphot). Total attached cells were counted 50-70 h. after isolation with a Coulter counter (model ZM, Coulter Electronics, Inc., Hialeah, FL). Cell counts of controls varied from 3.352×10^4 to 2.322×10^5 per well. Counting mononuclear cells at the time of isolation was not practical because of matrix and cell debris that could not be completely eliminated.

Bone slices exposed to osteoclasts for 20 h. after isolation were processed for staining by ultrasonication (twofold, 15 s, Branson) in 0.25M ammonium hydroxide before fixation (20 minutes) in 2.5% glutaraldehyde, 0.1M cacodylate, pH 7.4 (EM Supplies, Fort Washington, PA). Samples were dehydrated in ethanol (40, 70, and 100%; 5 minutes), air dried for 2 h., and then stained for 4 minutes with filtered 1% toluidine blue and 1% borax (Sigma, St. Louis, MO). Samples used to count osteoclasts were processed as earlier without ultrasonication in ammonium hydroxide.

A fluorescence microscope (Microphot, Nikon) was adapted for reflected light microscopy by inserting a $\lambda/4$ plate between cross polarizers in the epi mode. Fluorescence objectives of long working distance with adjustable correction collars (10 x, 20 x, Nikon) were fitted with rotatable $\lambda/4$ plates (Polaroid Corp., Massachusetts) mounted as the front element. Correction collars were necessary 20x objectives and higher to correct for the presence of the $\lambda/4$ plate and the absence of a coverslip. Coverslips were not used to eliminate stray reflections below the $\lambda/4$ plate. Immersion oil (Nikon) was added between the objective front lens and $\lambda/4$ to minimize reflections at this interface. Oil was not placed between objective and specimen.

Bone slices were scanned for resorption pits by rotating the $\lambda/4$ plate 0° - 45° with respect to the plane of polarization in epi-tungsten illumination. Alternatively, Hg illumination (HBO 100w, Nikon) was used with the $\lambda/4$ plate fixed at 45° while intermittently viewing stained images by transmission brightfield microscopy with an NCB 10 filter (Nikon).

- 190 -

Quantitation of resorbed areas of bone slices examined by bright-field, RLM, and SEM was achieved through digital image processing (Magiscan 2A, Joyce Loeb, NY) of video images (Newvicon or SIT, Dage-MTI, Inc. Michigan City, IN) fed through a NTSC/PAL digital standards converter (CEL P156, James Grunder and Assoc., Inc., Mission, Kansas).

Osteoclasts were processed for immunofluorescence by briefly rinsing coverslips in buffer S (60 mM Pipes, pH 6.9; 25 mM Hepes; 10 mM EGTA; and 2 mM $MgCl_2$) at 37°C. and then fixing for 2 minutes in buffer S+10% formaldehyde, pH 7.0. Cells were permeabilized in buffer S+0.5% Triton X-100 and then rinsed. Specimens were incubated (30 minutes) in appropriate antibody or rhodamine-phalloidine (Molecular Probes, Eugene, OR) followed by fluorescein goat antirabbit antibody (Cappel).

The bone slice assay is used to examine the effect of the compound of interest on the activity of isolated osteoclasts from rat long bones.

The number of resorption pits formed by osteoclasts after 1 day on consecutive cross sections of bovine femur was first compared to control samples by the method of Arnett and Dempster, *Endocrinology* 120:602-608, and then plotted as a function of concentration of the compound of interest.

The appropriateness of extrapolating data from this assay to utility and use in mammalian (including human) disease states is supported by the teaching found in Sato, M., *et al.*, *Journal of Bone and Mineral Research*, Vol. 5, No. 1, 1990. That article teaches that certain bisphosphonates have been used clinically and appear to be effective in the treatment of Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastases, and bone loss due to immobilization or sex hormone deficiency. These same bisphosphonates are then tested in the resorption pit assay described above to confirm a correlation between their known utility and positive performance in the assay.

- 191 -

EIB ASSAY

Duong *et al.*, *J. Bone Miner. Res.*, 8:S 378, describe a system for expressing the human integrin $\alpha_v\beta_3$. It has been suggested that the integrin is involved in the attachment of osteoclasts to bone matrix, since antibodies against the integrin, or RGD-containing molecules, such as echistatin (European Publication 382 451), can effectively block bone resorption.

Reaction Mixture:

- 10 1. 175 μ l TBS buffer (50 mM Tris•HCl pH 7.2, 150 mM NaCl, 1% BSA, 1 mM CaCl_2 , 1 mM MgCl_2).
2. 25 μ l cell extract (dilute with 100 mM octylglucoside buffer to give 2000 cpm/25 μ l).
3. ^{125}I -echistatin (25 μ l/50,000 cpm) (see EP 382 451).
- 15 4. 25 μ l buffer (total binding) or unlabeled echistatin (non-specific binding).

The reaction mixture was then incubated for 1 h at room temp. The unbound and the bound $\alpha_v\beta_3$ were separated by filtration using a Skatron Cell Harvester. The filters (prewet in 1.5% polyethyleneimine for 10 mins) were then washed with the wash buffer (50 mM Tris HCl, 1mM $\text{CaCl}_2/\text{MgCl}_2$, pH 7.2). The filter was then counted in a gamma counter.

25 OCFORM ASSAY

Osteoblast-like cells (1.8 cells), originally derived from mouse calvaria, are plated in CORNING 24 well tissue culture plates in α MEM medium containing ribo- and deoxyribonucleosides, 10% fetal bovine serum and penicillin-streptomycin. Cells are seeded at 30 40,000/well in the morning. In the afternoon, bone marrow cells are prepared from six week old male Balb/C mice as follows:

Mice are sacrificed, tibiae removed and placed in the above medium. The ends are cut off and the marrow is flushed out of the cavity into a tube with a 1 mL syringe with a 27.5 guage needle. The

- 192 -

marrow is suspended by pipetting up and down with a glass pasteur pipet. The suspension is passed through two layers of approximately 400 μm mesh stainless steel cloth. The resulting suspension is centrifuged at 350 x g for seven minutes. The pellet is resuspended, and a sample is diluted in 2% acetic acid to lyse the red cells. The remaining cells are counted in a hemacytometer. The cells are pelleted and resuspended at 1×10^6 cells/mL. 50 μL is added to each well of 1.8 cells to yield 50,000 cells/well and 1,25-dihydroxy-vitamin D₃(D₃) is added to each well to a final concentration of 10 nM. The cultures are incubated at 37°C in a humidified, 5% CO₂ atmosphere. After 48 h, the medium is changed. 72 h after the addition of bone marrow, test compounds are added with fresh medium containing D₃ to triplicate wells. Compounds are added again after 48 h with fresh medium containing D₃. After an additional 24 h the medium is removed, cells are fixed with 10% formaldehyde in phosphate buffered saline for 10 minutes at room temperature, followed by a 1-2 minute treatment with ethanol:acetone (1:1) and air dried. The cells are then stained for tartrate resistant acid phosphatase as follows:

The cells are stained for 10-15 minutes at room temperature with 50 mM acetate buffer, pH 5.0 containing 30 mM sodium tartrate, 0.3 mg/mL Fast Red Violet LB Salt and 0.1 mg/mL Naphthol AS -MX phosphate. After staining, the plates are washed extensively with dionized water and air dried. The number of multinucleated, positively staining cells are counted in each well.

The compounds of the invention have values in the range 0.5-500 nM in EIB and 1-1000 nM in OCFORM.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of bone disorders caused by resorption, or for other indications

- 193 -

for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of

5 formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is

10 reasonable.

- 194 -

WHAT IS CLAIMED IS:

1. A method of inhibiting the bone resorption activity of mammalian osteoclast cells comprising the step of administering a
 5 pharmacologically effective amount of a compound of the formula:

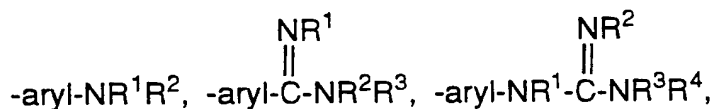
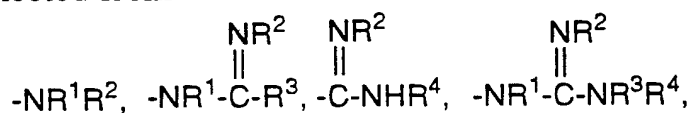


wherein:

10

Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 N atoms and either unsubstituted or substituted with one or more groups chosen from R¹ and R²;

- 15 X is selected from



or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted
 20 with R¹³, R¹⁴, R¹⁵ or R¹⁶;

Y is selected from the group consisting of

C₀₋₈ alkylene,

C₃₋₁₀ cycloalkyl,

25

C₀₋₈ alkylene-NR³-CO-C₀₋₈ alkylene,

C₀₋₈ alkylene-CONR³-C₀₋₈ alkylene,

C₀₋₈ alkylene-O-C₀₋₈ alkylene,

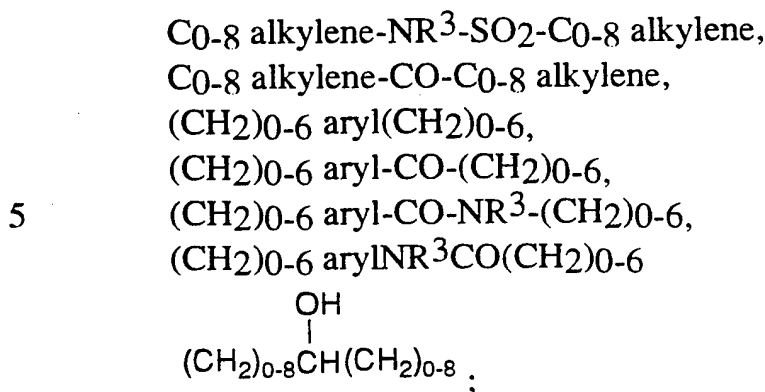
C₀₋₈ alkylene-NR¹-C₀₋₈ alkylene,

C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,

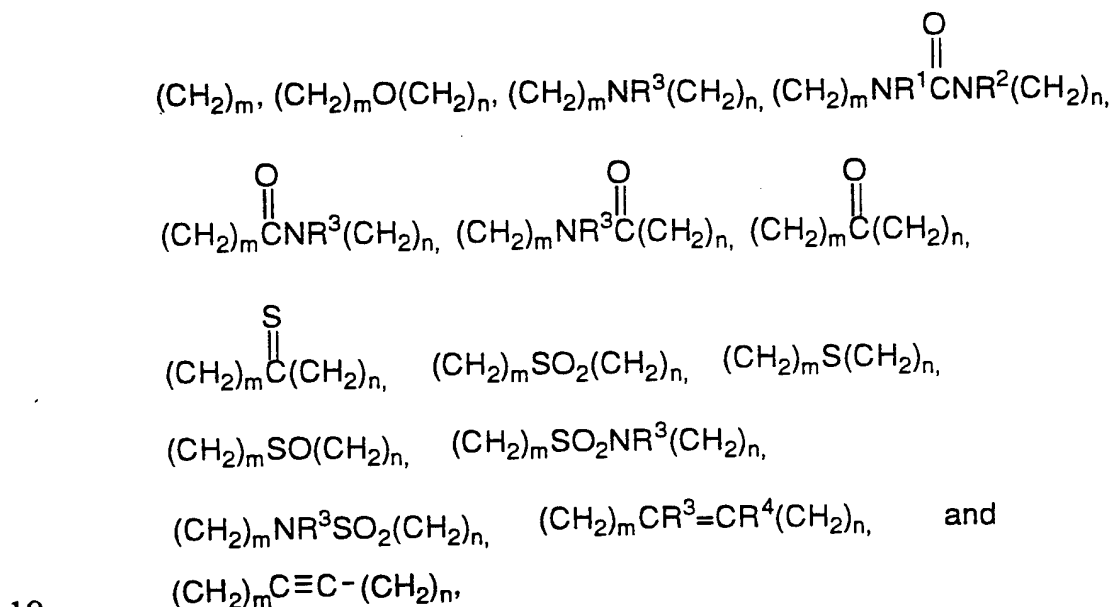
30

C₀₋₈ alkylene-SO₂-NR³-C₀₋₈ alkylene,

- 195 -

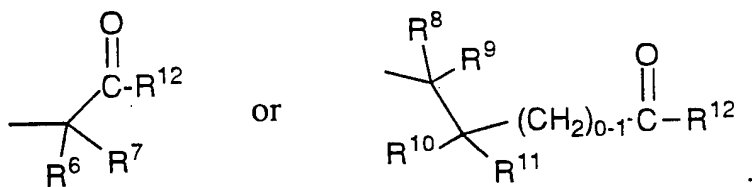


Z and A are each independently selected from the group consisting of



where m and n are integers independently chosen from 0-6;

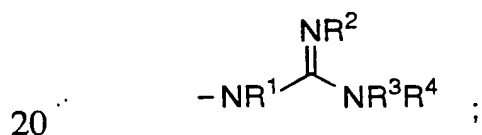
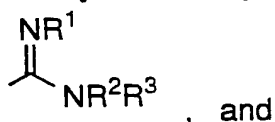
B is selected from



- 196 -

R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- hydrogen,
 halogen,
 5 C₁-10 alkyl,
 aryl C₀-8 alkyl,
 amino C₀-8 alkyl,
 C₁-3 acylamino C₀-8 alkyl,
 C₁-6 alkylamino C₀-8 alkyl,
 10 C₁-6 dialkylamino C₀-8 alkyl,
 aryl C₀-6 alkylamino C₀-6 alkyl,
 C₁-4 alkoxyamino C₀-8 alkyl,
 hydroxy C₁-6 alkylamino C₀-8 alkyl,
 C₁-4 alkoxy C₀-6 alkyl,
 15 carboxy C₀-6 alkyl,
 C₁-4 alkoxycarbonyl C₀-6 alkyl,
 carboxy C₀-6 alkyloxy,
 hydroxy C₁-6 alkylamino C₀-6 alkyl,
 hydroxy C₀-6 alkyl,



R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from

- hydrogen,
 fluorine,
 25 C₁-8 alkyl,
 hydroxyl,
 hydroxy C₁-6 alkyl,
 carboxy C₀-6 alkyl,
 C₁-6 alkyloxy,

- 197 -

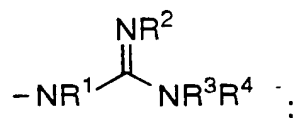
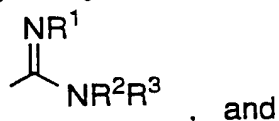
- 5 C1-6 alkylcarbonyl,
aryl C0-6 alkylcarbonyl,
C1-6 alkylcarbonyloxy,
aryl C0-6 alkylcarbonyloxy,
C1-6 alkylaminocarbonyloxy,
C3-8 cycloalkyl,
aryl C0-6 alkyl,
C0-6 alkylamino C0-6 alkyl,
C0-6 dialkylamino C0-6 alkyl,
10 C1-8 alkylsulfonylamino C0-6 alkyl,
aryl C0-6 alkylsulfonylamino C0-6 alkyl,
C1-8 alkyloxy carbonylamino C0-8 alkyl,
aryl C0-8 alkyloxy carbonylamino C0-8 alkyl,
C1-8 alkylcarbonylamino C0-6 alkyl,
15 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
C0-8 alkylaminosulfonylamino C0-6 alkyl,
aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
20 C1-6 alkylsulfonyl C0-6 alkyl,
aryl C0-6 alkylsulfonyl C0-6 alkyl,
C1-6 alkylcarbonyl C0-6 alkyl,
aryl C0-6 alkylcarbonyl C0-6 alkyl,
C1-6 alkylthiocarbonylamino C0-6 alkyl, and
25 aryl C0-6 alkylthiocarbonylamino C0-6 alkyl
wherein the alkyl, aryl, or N atoms may be unsubstituted or
substituted with one or more substituents selected from R¹ and
R²;
- 30 R¹² is selected from
hydroxy,
C1-8 alkyloxy,
aryl C0-6 alkyloxy,
C1-8 alkylcarbonyloxy C1-4 alkyloxy,

- 198 -

aryl C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 C₁-6 dialkylaminocarbonylmethyloxy,
 aryl C₁-6 dialkylaminocarbonylmethyloxy or
 an L- or D-amino acid joined by an amide linkage and
 5 wherein the carboxylic acid moiety of said amino acid
 is as the free acid or is esterified by C₁-6 alkyl; and

R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from the group
 consisting of

10 hydrogen,
 C₁-10 alkyl,
 aryl C₀-8 alkyl,
 oxo,
 thio,
 15 amino C₀-8 alkyl,
 C₁-3 acylamino C₀-8 alkyl,
 C₁-6 alkylamino C₀-8 alkyl,
 C₁-6 dialkylamino C₀-8 alkyl,
 aryl C₀-6 alkylamino C₀-6 alkyl,
 20 C₁-4 alkoxyamino C₀-8 alkyl,
 hydroxy C₁-6 alkylamino C₀-8 alkyl,
 C₁-4 alkoxy C₀-6 alkyl,
 carboxy C₀-6 alkyl,
 C₁-4 alkoxycarbonyl C₀-6 alkyl,
 25 carboxy C₀-6 alkyloxy,
 hydroxy C₁-6 alkylamino C₀-6 alkyl,
 hydroxy C₀-6 alkyl,



- 199 -

and the pharmaceutically acceptable salts thereof .

2. A method of claim 1 wherein the compound has the formula:

5



wherein:

10 Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 N atoms and either unsubstituted or substituted with one or more groups chosen from R¹ and R²;

X is selected from

15
$$\begin{array}{c} \text{NR}^2 \quad \text{NR}^2 \quad \text{NR}^2 \\ \parallel \quad \parallel \quad \parallel \\ -\text{NR}^1\text{R}^2, -\text{NR}^1-\text{C}-\text{R}^3, -\text{C}-\text{NHR}^4, -\text{NR}^1-\text{C}-\text{NR}^3\text{R}^4, \\ \text{NR}^1 \quad \text{NR}^2 \\ \parallel \quad \parallel \\ -\text{aryl}-\text{NR}^1\text{R}^2, -\text{aryl}-\text{C}-\text{NR}^1\text{R}^2, -\text{aryl}-\text{NR}^1-\text{C}-\text{NR}^3\text{R}^4, \end{array}$$

or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R¹³, R¹⁴, R¹⁵ or R¹⁶;

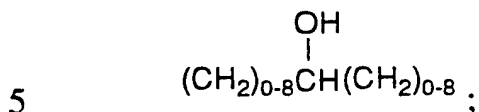
20

Y is selected from the group consisting of

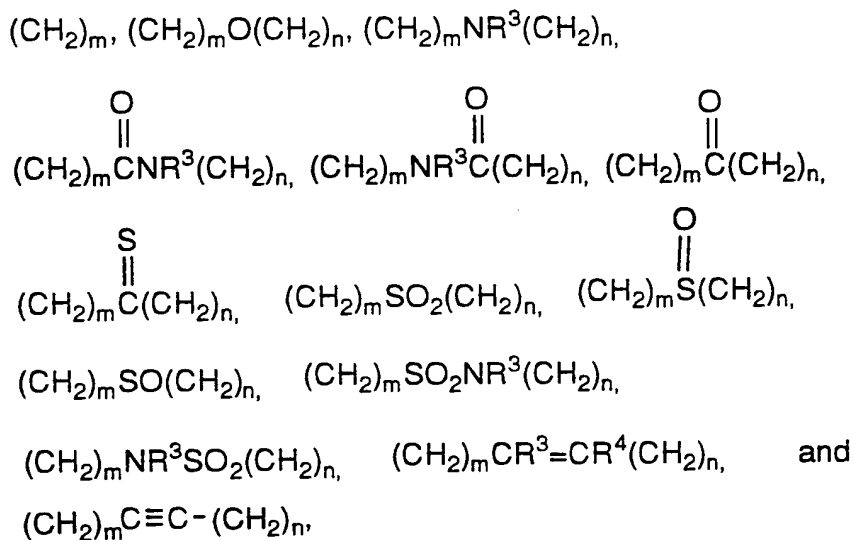
C0-8 alkylene,
C3-10 cycloalkyl,
C0-8 alkylene-NR³-CO-C0-8 alkylene,
25 C0-8 alkylene-CONR³-C0-8 alkylene,
C0-8 alkylene-O-C0-8 alkylene,
C0-8 alkylene-NR¹-C0-8 alkylene,
C0-8 alkylene-S(O)₀₋₂-C0-8 alkylene,
C0-8 alkylene-SO₂-NR³-C0-8 alkylene,
30 C0-8 alkylene-NR³-SO₂-C0-8 alkylene,

- 200 -

C0-8 alkylene-CO-C0-8 alkylene,
 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-NH-(CH₂)₀₋₆, and



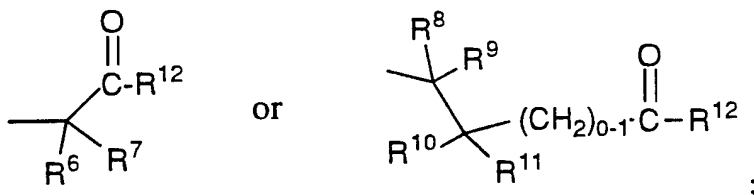
Z and A are each independently selected from the group consisting of



where m and n are integers independently chosen from 0-6;

10

B is selected from



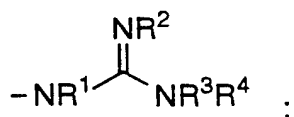
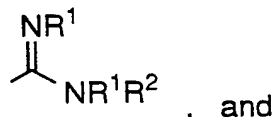
R¹, R², R³ and R⁴ are each independently selected from the group consisting of

15

hydrogen,

- 201 -

- halogen,
 C1-10 alkyl,
 aryl C0-8 alkyl,
 amino C0-8 alkyl,
 5 C1-3 acylamino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,
 aryl C0-6 alkylamino C0-6 alkyl,
 C1-4 alkoxyamino C0-8 alkyl,
 10 hydroxy C1-6 alkylamino C0-8 alkyl,
 C1-4 alkoxy C0-6 alkyl,
 carboxy C0-6 alkyl,
 C1-4 alkoxycarbonyl C0-6 alkyl,
 carboxy C0-6 alkyloxy,
 15 hydroxy C1-6 alkylamino C0-6 alkyl,
 hydroxy C0-6 alkyl,



- R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are each independently selected from
 20 hydrogen,
 fluorine,
 C1-8 alkyl,
 hydroxyl,
 hydroxy C1-6 alkyl,
 25 carboxy C0-6 alkyl,
 C1-6 alkyloxy,
 C1-6 alkylcarbonyl,
 aryl C0-6 alkylcarbonyl,
 C1-6 alkylcarbonyloxy,

- 202 -

aryl C0-6 alkylcarbonyloxy,
C1-6 alkylaminocarbonyloxy,
C3-8 cycloalkyl,
aryl C0-6 alkyl,
5 C0-6 alkylamino C0-6 alkyl,
C0-6 dialkylamino C0-6 alkyl,
C1-8 alkylsulfonylamino C0-6 alkyl,
aryl C0-6 alkylsulfonylamino C0-6 alkyl,
C1-8 alkyloxy carbonylamino C0-8 alkyl,
10 aryl C0-8 alkyloxy carbonylamino C0-8 alkyl,
C1-8 alkylcarbonylamino C0-6 alkyl,
aryl C0-6 alkylcarbonylamino C0-6 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
15 C0-8 alkylaminosulfonylamino C0-6 alkyl,
aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
C1-6 alkylsulfonyl C0-6 alkyl,
aryl C0-6 alkylsulfonyl C0-6 alkyl,
C1-6 alkylcarbonyl C0-6 alkyl,
20 aryl C0-6 alkylcarbonyl C0-6 alkyl,
C1-6 alkylthiocarbonylamino C0-6 alkyl, and
aryl C0-6 alkylthiocarbonylamino C0-6 alkyl
wherein the alkyl or aryl groups may be unsubstituted or
substituted with one or more substituents selected from R¹ and
25 R²;

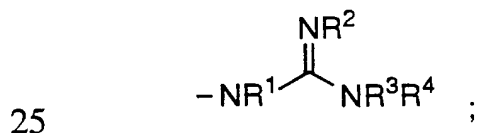
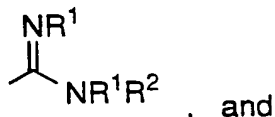
R¹² is selected from
hydroxy,
C1-8 alkyloxy,
30 aryl C0-6 alkyloxy,
C1-8 alkylcarbonyloxy C1-4 alkyloxy,
aryl C1-8 alkylcarbonyloxy C1-4 alkyloxy,
C1-6 dialkylaminocarbonylmethyloxy,
aryl C1-6 dialkylaminocarbonylmethyloxy or

- 203 -

an L- or D-amino acid joined by an amide linkage and wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C₁₋₆ alkyl; and

- 5 R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from the group consisting of

hydrogen,
 C₁₋₁₀ alkyl,
 aryl C₀₋₈ alkyl,
 10 oxo,
 thio,
 amino C₀₋₈ alkyl,
 C₁₋₃ acylamino C₀₋₈ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 15 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₁₋₄ alkoxyamino C₀₋₈ alkyl,
 hydroxy C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 20 carboxy C₀₋₆ alkyl,
 C₁₋₄ alkoxy carbonyl C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyloxy,
 hydroxy C₁₋₆ alkylamino C₀₋₆ alkyl,
 hydroxy C₀₋₆ alkyl,



and the pharmaceutically acceptable salts thereof .

- 204 -

3. The method of Claim 2, wherein Aryl is a 6-membered aromatic ring containing 0, 1 or 2 N atoms and either unsubstituted or substituted with one or more groups chosen from R¹ and R²;

5

X is defined in claim 2;

Y is selected from

C0-8 alkylene,
 C0-8 alkylene-NR³-CO-C0-8 alkylene,
 10 C0-8 alkylene-CONR³-C0-8 alkylene,
 C0-8 alkylene-O-C0-8 alkylene,
 C0-8 alkylene-NR¹-C0-8 alkylene,
 C0-8 alkylene-S(O)₀₋₂-C0-8 alkylene,
 C0-8 alkylene-SO₂-NR³-C0-8 alkylene, or
 15 C0-6 alkylene-aryl-C0-6 alkylene;

Z and A are each independently selected from the group consisting of

(CH₂)_m, (CH₂)_mO(CH₂)_n, (CH₂)_m-NR³-(CH₂)_n,

$(\text{CH}_2)_m \overset{\text{O}}{\parallel} \text{CNR}^3 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^3 \overset{\text{O}}{\parallel} \text{C} (\text{CH}_2)_n$,

$(\text{CH}_2)_m \overset{\text{O}}{\parallel} \text{C} (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{SO}_2 (\text{CH}_2)_n$,

$(\text{CH}_2)_m \text{SO}_2 \text{NR}^3 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^3 \text{SO}_2 (\text{CH}_2)_n$,

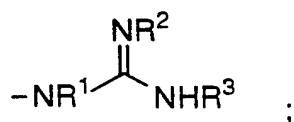
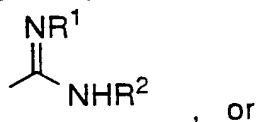
and $(\text{CH}_2)_m \text{C} \equiv \text{C} - (\text{CH}_2)_n$,

wherein m and n are independently chosen from 0-6;

20 R¹, R², R³ and R⁴ are each independently selected from
 hydrogen,
 C1-10 alkyl,
 aryl C0-8 alkyl,

- 205 -

amino C0-8 alkyl,
 C1-3 acylamino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,
 5 C1-4 alkyloxy C0-6 alkyl,
 carboxy C0-6 alkyl,
 C1-4 alkyloxycarbonyl C0-6 alkyl,
 carboxy C0-6 alkyloxy,
 hydroxy C0-6 alkyl,



R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are independently selected from the group consisting of

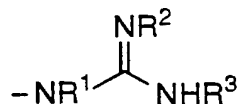
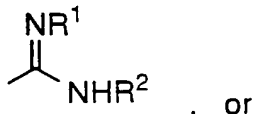
15 hydrogen,
 hydroxyl,
 fluorine,
 C1-8 alkyl,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 20 C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8 alkyl,
 25 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
 C1-8 alkylcarbonylamino C0-6 alkyl,
 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonylamino C0-6 alkyl,
 aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,

- 206 -

C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 5 C1-6 alkylcarbonyl C0-6 alkyl, and
 aryl C0-6 alkylcarbonyl C0-6 alkyl;

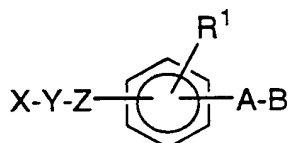
R¹² is selected from the group consisting of
 hydroxy,
 10 C1-8 alkyloxy,
 aryl C0-6 alkyloxy,
 C1-8 alkylcarbonyloxy C1-4 alkyloxy, and
 aryl C0-8 alkylcarbonyloxy C1-4 alkyloxy; and

15 R¹³, R¹⁴, R¹⁵ and R¹⁶ are each independently selected from
 hydrogen,
 C1-10 alkyl,
 aryl C0-8 alkyl,
 oxo,
 20 amino C0-8 alkyl,
 C1-3 acylamino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,
 C1-4 alkyloxy C0-6 alkyl,
 25 carboxy C0-6 alkyl,
 C1-4 alkyloxycarbonyl C0-6 alkyl,
 carboxy C0-6 alkyloxy,
 hydroxy C0-6 alkyl,



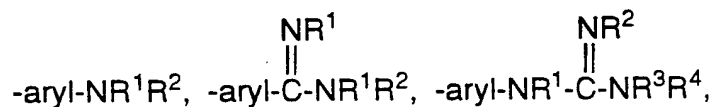
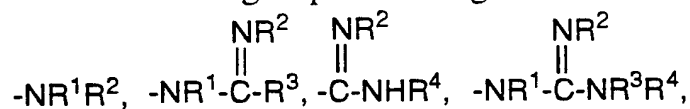
- 207 -

4. The method of Claim 3, wherein the compound has the formula:



5 wherein:

X is selected from the group consisting of



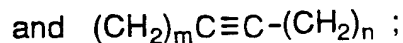
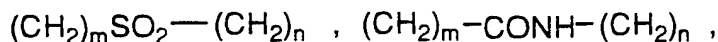
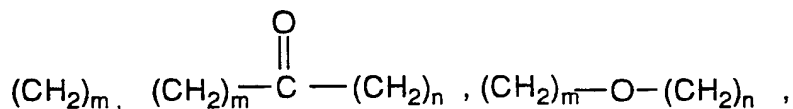
10 or a 5- to 10- membered aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N and S and either unsubstituted or substituted with R¹³, R¹⁴, R¹⁵ or R¹⁶;

Y is selected from the group consisting of

15 C0-8 alkylene,
C0-8 alkylene-NR³-CO-C0-8 alkylene,
C0-8 alkylene-CONR³-C0-8 alkylene,
C0-8 alkylene-O-C0-8 alkylene,
C0-8 alkylene-NR¹-C0-8 alkylene and
20 C0-8 alkylene-S(O)₀₋₂-C0-8 alkylene;

Z and A are each independently selected from the group consisting of

- 208 -



wherein m and n are independently chosen from 0-6;

B is defined as in Claim 2;

R¹, R², R³ or R⁴, are each independently selected from the group

5 consisting of

hydrogen,

C₁₋₁₀ alkyl,

aryl C₀₋₈ alkyl,

C₁₋₄ alkyloxy C₀₋₆ alkyl,

10 C₁₋₄ alkoxy carbonyl C₀₋₆ alkyl,

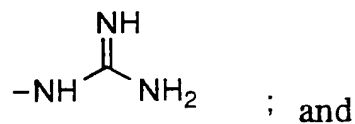
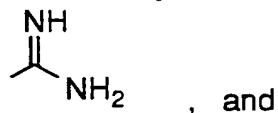
carboxy C₀₋₆ alkyl,

hydroxy C₀₋₆ alkyl,

amino C₀₋₈ alkyl,

C₁₋₆ alkylamino C₀₋₈ alkyl,

15 C₁₋₆ dialkylamino C₀₋₈ alkyl,



R⁶-R¹² are defined as in Claim 3;

R¹³, R¹⁴, R¹⁵ or R¹⁶, are each independently selected from the group

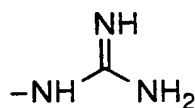
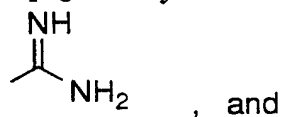
20 consisting of

hydrogen,

C₁₋₁₀ alkyl,

- 209 -

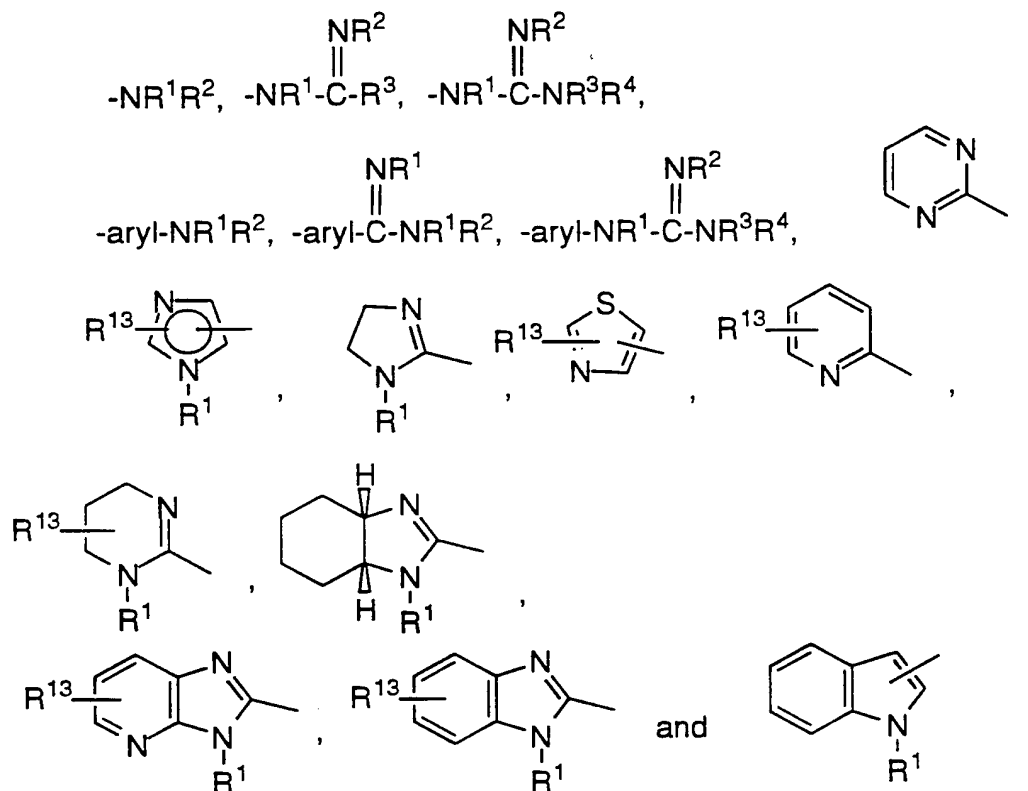
aryl C0-8 alkyl,
oxo,
C1-4 alkyloxy C0-6 alkyl,
C1-4 alkoxy carbonyl C0-6 alkyl,
5 carboxy C0-6 alkyl,
hydroxy C0-6 alkyl,
amino C0-8 alkyl,
C1-6 alkylamino C0-8 alkyl,
C1-6 dialkylamino C0-8 alkyl,



5. The method of Claim 4, wherein

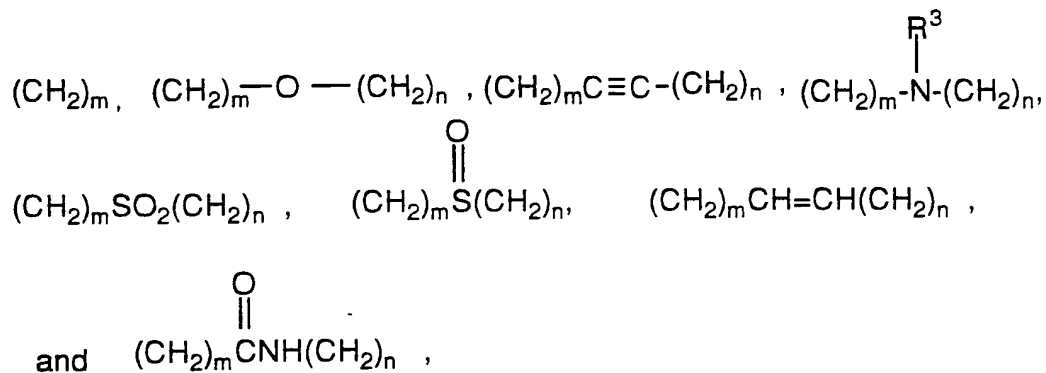
X is selected from the group consisting of

- 210 -



Y is selected from the group consisting of
 C0-8 alkylene,
 C0-8 alkylene-NR³-CO-C0-8 alkylene,
 C0-8 alkylene-O-C0-8 alkylene and
 C0-8 alkylene-NR¹-C0-8 alkylene;

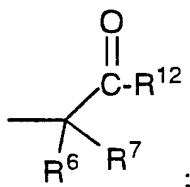
Z and A are each independently selected from the group consisting of



- 211 -

wherein m and n are independently chosen from 0-6;

B is



- 5 R¹, R², R³ and R⁴ are each independently selected from the group consisting of
- hydrogen,
 - C₁₋₄ alkoxy C₀₋₆ alkyl,
 - C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 - C₁₋₆ alkylamino C₀₋₈ alkyl,
 - 10 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 - amino C₀₋₈ alkyl and
 - aryl C₀₋₈ alkyl;

- 15 R⁶ and R⁷ are each independently selected from the group consisting of:
- hydrogen,
 - C₀₋₆ alkylamino C₀₋₆ alkyl,
 - C₀₋₆ dialkylamino C₀₋₆ alkyl,
 - aryl C₀₋₆ alkylloxycarbonylamino C₀₋₆ alkyl,
 - aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl and
 - 20 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl;

- R¹² is selected from the group consisting of
- hydroxy and
 - C₁₋₈ alkyloxy; and

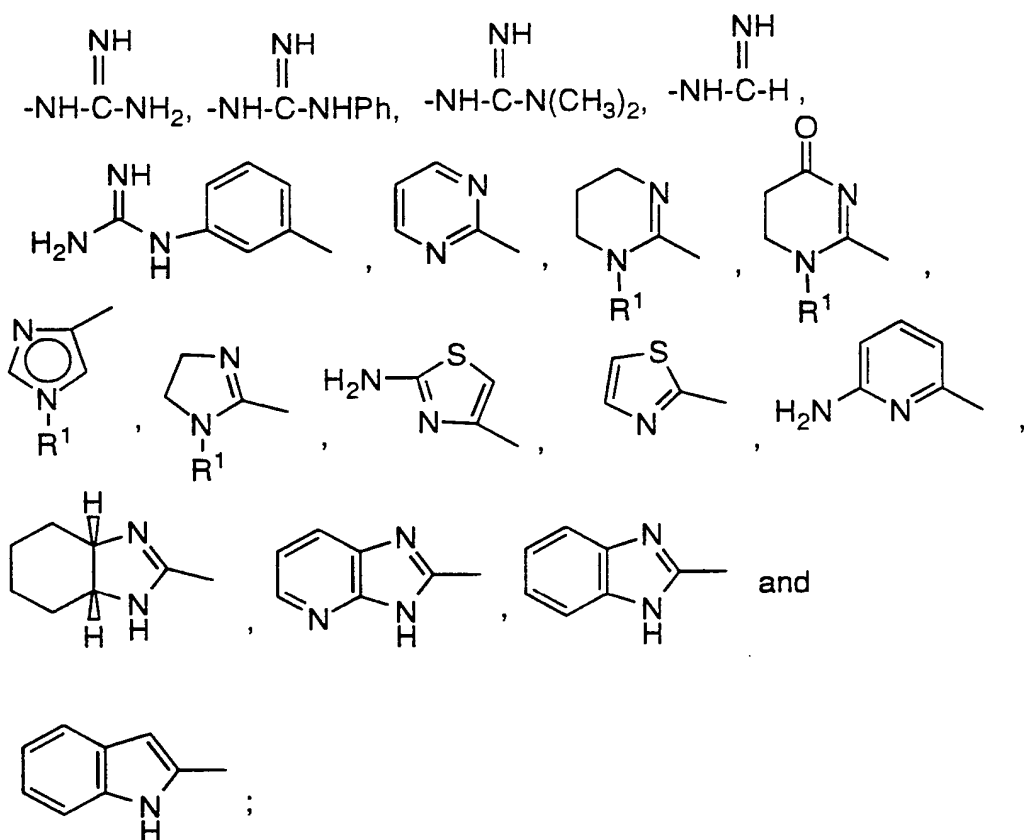
- 25 R¹³ is selected from the group consisting of
- hydrogen,
 - C₁₋₄ alkoxy C₀₋₆ alkyl,
 - C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 - 30 C₁₋₆ alkylamino C₀₋₈ alkyl,

- 212 -

**C1-6 dialkylamino C0-8 alkyl,
amino C0-8 alkyl,
oxo and
aryl C0-8 alkyl.**

5

6. The method of Claim 5, wherein X is selected from the group consisting of



10 Y is selected from the group consisting of
C0-2 alkylene,
C0-2 alkylene-NH-CO-,
C0-5 alkylene-O-C0-1 alkylene and
-NH-C2-4 alkylene;

15 R⁶ and R⁷ are each independently selected from the group consisting of

- 213 -

- hydrogen,
-NHCbz,
-NH₂SO₂Ph,
-NHC(O)-Ph, and
5 -N(CH₃)-SO₂Ph.

7. The method of Claim 6, wherein the compound is selected from the group consisting of:

- 10 4-(2-Guanidinoethyloxy)benzoyl-2(S)-benzyloxycarbonylamino-β-alanine,
4-(2-Guanidinoethyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,
15 2(S)-Phenylsulfonylamino-3-[4-(4-guanidinobutyloxy)phenyl]-propionic acid,
2(S)-(N-Benzyloxycarbonylamino)-3-[4-(5-guanidopentyloxy)phenyl]-propionic acid,
20 4-(3-Guanidinopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,
4-(3-Formamidinopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,
25 3-Methoxy-4-(3-guanidinopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,
30 3-Methoxy-4-(3-aminopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,
3-(3-Guanidinopropyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

- 214 -

- 4-[2-(N-Phenylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-
β-alanine,
- 5 4-[2-(N,N-Dimethylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,
- 4-(Guanidinophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino-β-
alanine,
- 10 4-[2-(Guanidino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino-β-
alanine,
- 15 3-[2-(Guanidino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,
- 4-[2-(1-Benzylimidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,
- 20 4-[2-(Imidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-
alanine,
- 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-
β-alanine t-butyl ester,
- 25 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,
- 4-[2-(N-(2-Imidazolin-2-yl)aminoethyloxy]benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,
- 30 2(S)-Phenylsulfonylamino-3-[4-(4-(N-imidazolin-2-yl)aminobutyloxy)-
phenyl]propionic acid,

- 215 -

- 4-[2-[N-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]amino]-ethyloxybenzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 5 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 10 4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester,
- 4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 15 4-[2(S)-(N-(2-Imidazolin-2-yl)amino)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 20 4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino- β -alanine,
- 25 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonylamino- β -alanine,
- 30 Methyl 2(S)-benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)-phenyl]propionate,
- 2(S)-Benzoylamino-3-[4-(4-pyrimidin-2-ylamino)butyloxy)phenyl]-propionic acid,

- 216 -

2(S)-Benzoylamino-3-[4-(4-(3,4,5,6-tetrahydropyrimidin-2-ylamino)-
butyloxy)phenyl]propionic acid,

5 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-(N-methyl)-phenyl-
sulfonylamino- β -alanine t-butyl ester,

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-(N-methyl)-phenyl-
sulfonylamino- β -alanine,

10

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-
(N-methyl)-phenylsulfonylamino- β -alanine,

15 4-[2-(N-(5,6-Dihydro-4-keto-1(H)-pyrimidin-2-yl)amino)ethyloxy]-
benzoyl-2(S)-phenylsulfonylamino- β -alanine,

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino- β -
alanine t-butyl ester,

20 4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino- β -
alanine,

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -
alanine,

25

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenyl-
sulfonylamino- β -alanine t-butyl ester,

30 4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-
 β -alanine,

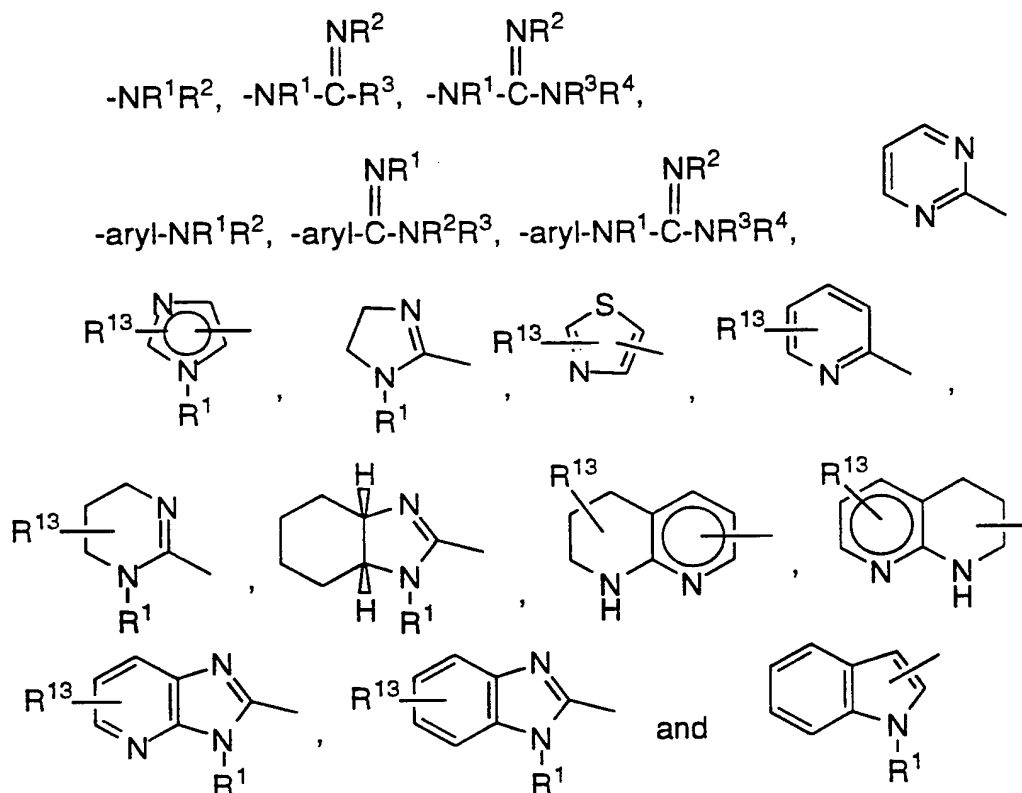
4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine
methyl ester,

- 217 -

- 4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[3-[N-1H-Benzimidazol-2-yl)amino]propyloxy]benzoyl-2(S)-
phenylsulfonylamino- β -alanine,
- 5 4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 10 4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 15 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β -alanine,
- 20 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 25 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine ethyl ester,
- 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 30 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine
- and their pharmaceutically acceptable salts.

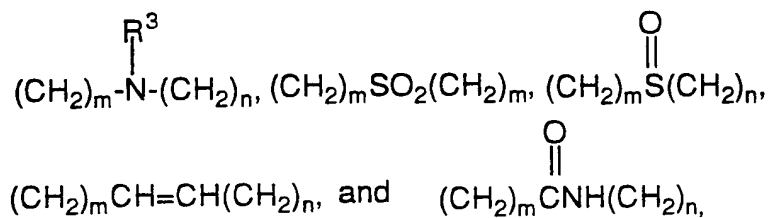
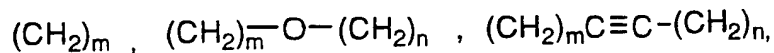
8. A method of claim 1, wherein X of the compound is selected from the group consisting of

- 218 -



Y is selected from the group consisting of
C0-8 alkylene,
C0-8 alkylene-NR³-CO-C0-8 alkylene,
5 C0-8 alkylene-O-C0-8 alkylene and
C0-8 alkylene-NR¹-C0-8 alkylene;

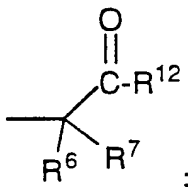
∴ Z and A are each independently selected from the group consisting of



10 wherein m and n are independently chosen from 0-6;

- 219 -

B is



R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- 5 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 10 amino C₀₋₈ alkyl and
 aryl C₀₋₈ alkyl;

R⁶ and R⁷ are each independently selected from the group consisting of:

- hydrogen,
 15 C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkyloxycarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl and
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl;

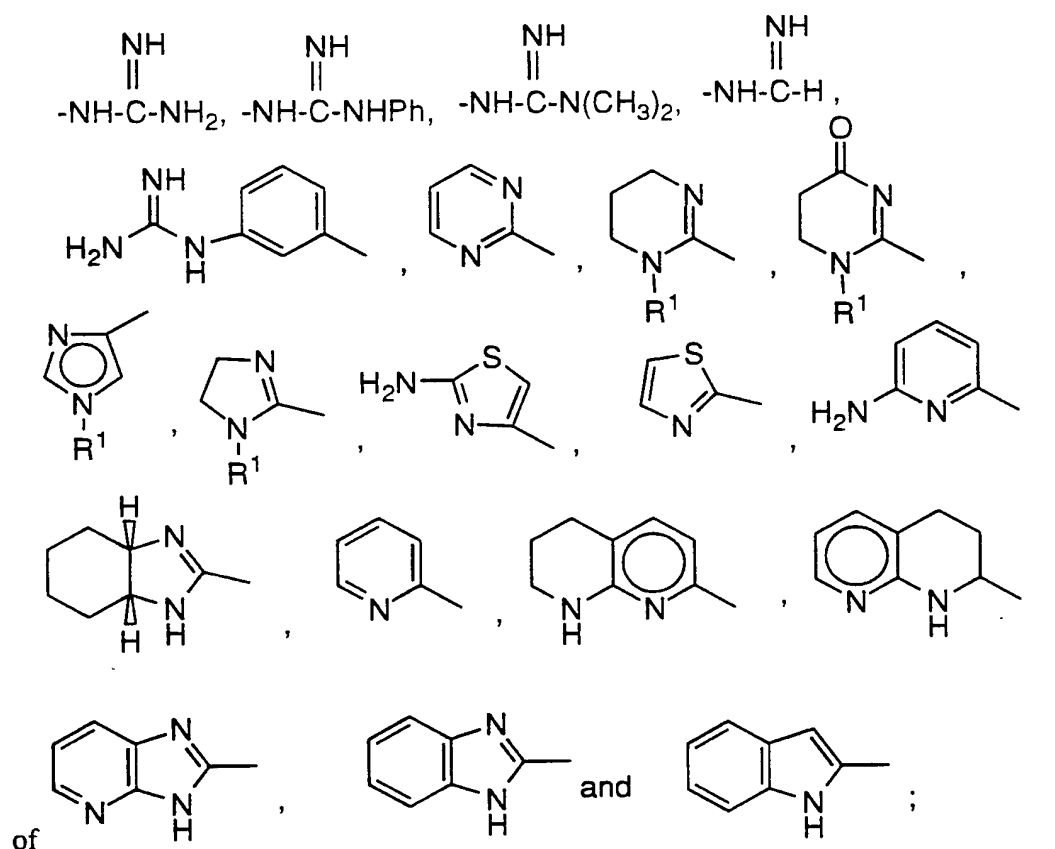
- 20 R¹² is selected from the group consisting of
 hydroxy and
 C₁₋₈ alkyloxy; and

- 25 R¹³ is selected from the group consisting of
 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 30 C₁₋₆ dialkylamino C₀₋₈ alkyl,

- 220 -

amino C0-8 alkyl,
 oxo and
 aryl C0-8 alkyl.

9. A method of claim 8 wherein X of the compound is
 5 selected from the group consisting of



A and B are defined as in claim 8;

Y is selected from the group consisting of

- 10 C0-2 alkylene,
 C0-2 alkylene-NH-CO-,
 C0-5 alkylene-O-C0-1 alkylene and
 -NH-C2-4 alkylene; and

- 221 -

R⁶ and R⁷ are each independently selected from the group consisting of
hydrogen,
-NHCbz,
-NH₂SO₂Ph,
5 -NHC(O)-Ph, and
-N(CH₃)-SO₂Ph.

10. A method of claim 9 wherein the compound is selected from the group consisting of
- 10 4-[2-(1H-Imidazo[4,5-6]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine t-butyl ester,
- 15 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine,
- 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine,
- 20 4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butylester,
- 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester,
- 25 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,
- 4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine ethyl ester,
- 30 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine ethyl ester,

- 222 -

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-
[1(S)10-camphorsulfonylamido] β -alanine ethyl ester,

5 4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)-
[1(S)10-camphorsulfonylamido] β -alanine,

4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido-
 β -alanine ethyl ester,

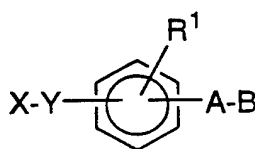
10 4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido-
 β -alanine trifluoroacetate,

4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonamido-
 β -alanine trifluoroacetate,

15 4-[3-[N-(1H-Benzimidazo-2-yl)amino]propoxy]benzoyl-2(S)-
phenylsulfonylamino- β -alanine t-butyl ester, and

20 4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-2(S)-
phenylsulfonylamino- β -alanine.

11. A compound of the formula

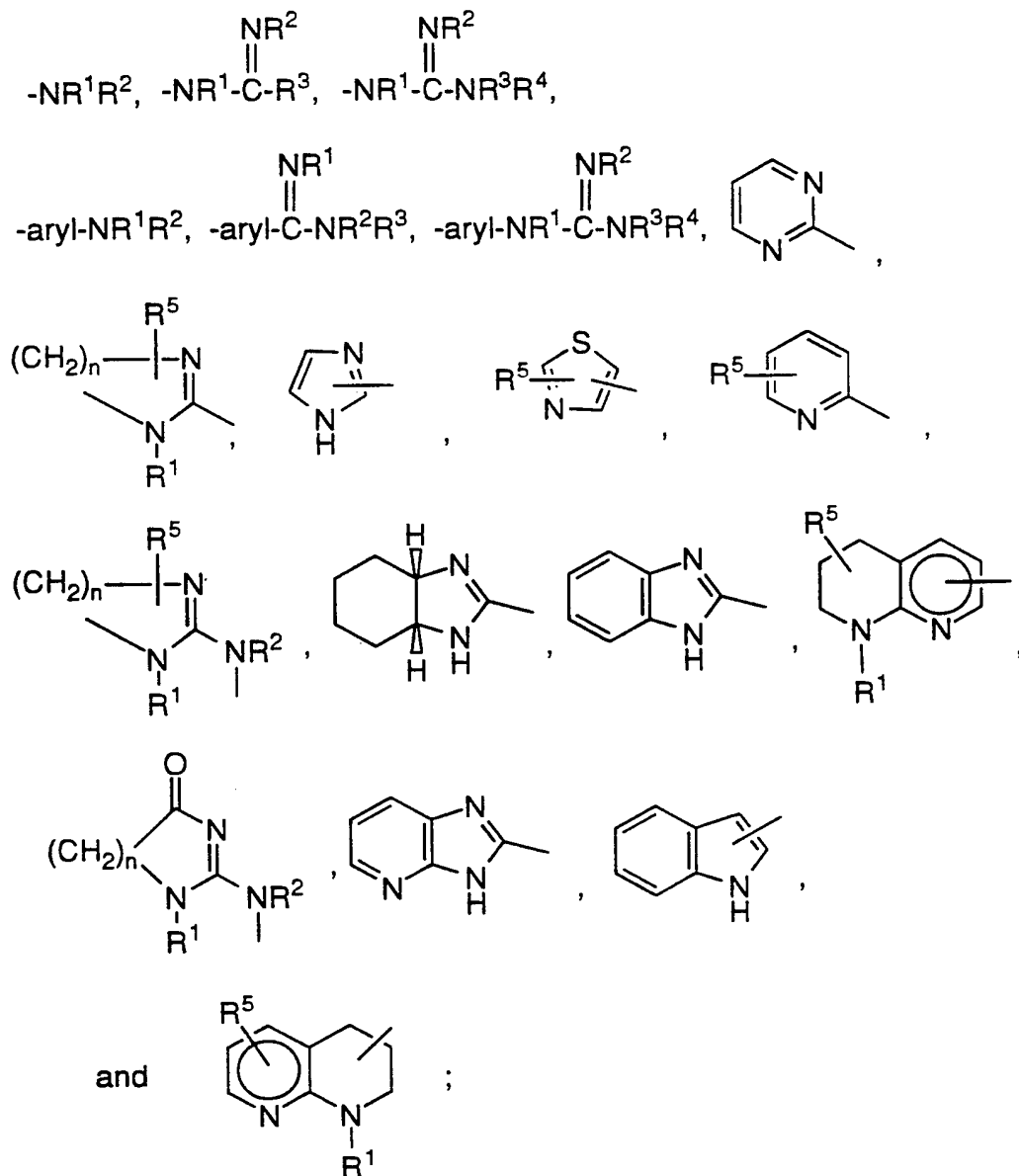


wherein

25

X is selected from the group consisting of

- 223 -



Y is selected from the group consisting of

C1-8 alkylene,

$(\text{CH}_2)_m\text{-C}\equiv\text{C}(\text{CH}_2)_n$,

$(\text{CH}_2)_m\text{CR}^1=\text{CR}^2(\text{CH}_2)_n$,

$(\text{CH}_2)_m\text{CR}^1=\text{CR}^2(\text{CH}_2)_n\text{O}$,

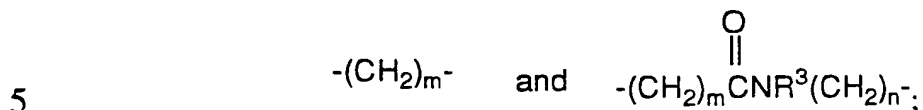
C0-8 alkylene-NR³-CO-C0-8 alkylene,

C0-8 alkylene-O-C0-8 alkylene,

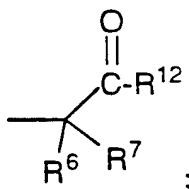
- 224 -

C₀₋₈ alkylene-NR³-C₀₋₈ alkylene and
 C₀₋₈ alkylene-NR³-C₀₋₈ alkylene-O-;

A is selected from the group consisting of



B is



R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- 10 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 15 amino C₀₋₈ alkyl and
 aryl C₀₋₈ alkyl;

R⁵ is selected from the group consisting of

- 20 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 amino C₀₋₈ alkyl,
 25 oxo and
 aryl C₀₋₈ alkyl;

- 225 -

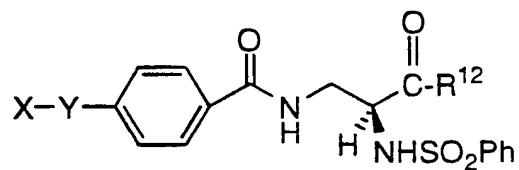
R⁶ and R⁷ are each independently selected from the group consisting of:

- hydrogen,
 C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 5 aryl C0-6 alkyloxycarbonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl and
 aryl C0-6 alkylcarbonylamino C0-6 alkyl;

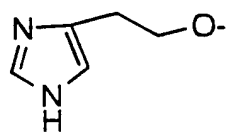
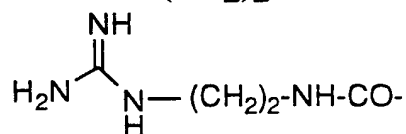
- R¹² is selected from the group consisting of
 10 hydroxy,
 C1-8 alkyloxy,
 C1-6 dialkylaminocarbonylmethoxy and
 aryl C1-6 dialkylaminocarbonylmethoxy; and

- 15 m and n are integers independently chosen from 0-6;

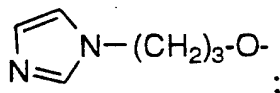
provided that when the compound is



- wherein R¹² is hydroxy or C1-4 alkyloxy, then X-Y is not
 20 NH₂-(CH₂)₂-NH-CO-,
 BOC-HN-(CH₂)₂-NH-CO-,



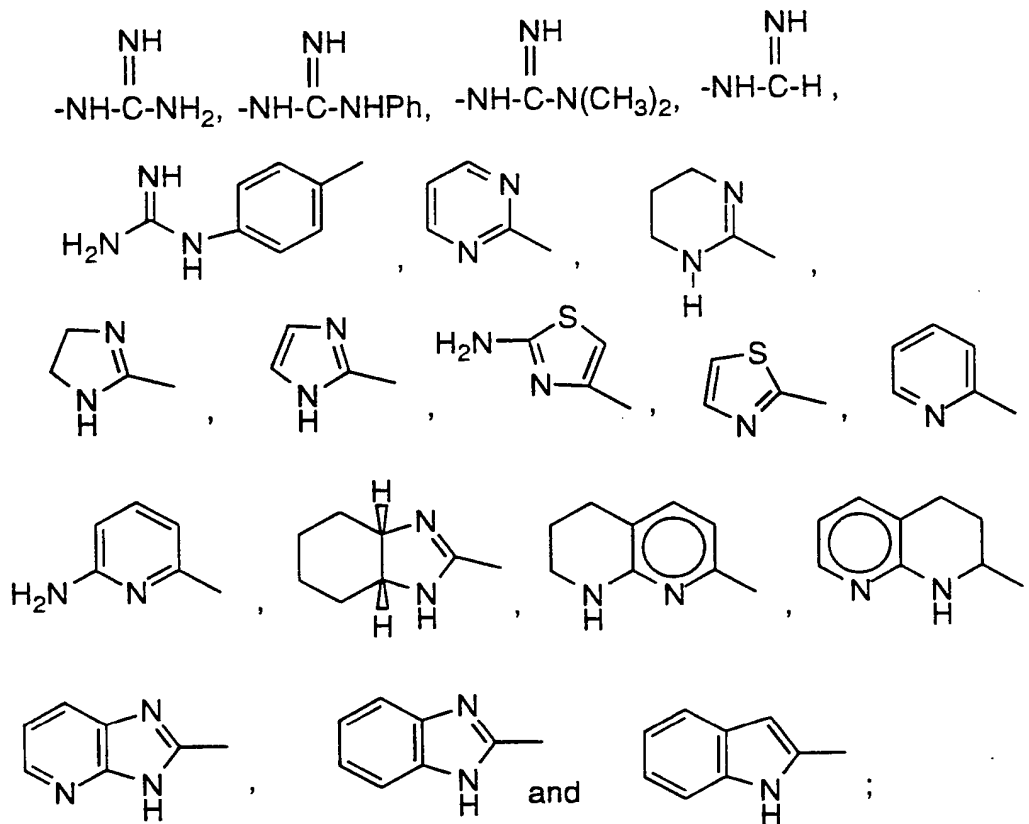
or



- 226 -

and the pharmaceutically acceptable salts thereof.

12. A compound of claim 11, wherein
X is selected from the group consisting of



5

Y is selected from the group consisting of

C₁₋₃ alkylene,

-C≡C-,

C₀₋₂ alkylene-NH-CO-,

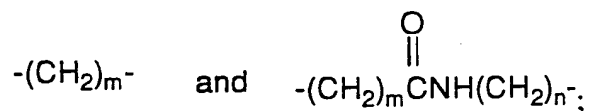
10 C₀₋₅ alkylene-O-C₀₋₁ alkylene

-NH-C₂₋₄ alkylene and

-NH-C₂₋₄ alkylene-O-;

A is selected from the group consisting of

- 227 -



R^1 is selected from the group consisting of
hydrogen and

C_{1-4} alkoxy;

5 R^6 and R^7 are each independently selected from the group consisting of
hydrogen,

$-\text{NHCbz}$,

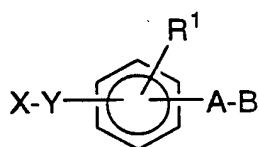
$-\text{NHSO}_2\text{Ph}$,

$-\text{NHC(O)-Ph}$ and

10 $-\text{N(CH}_3\text{)-SO}_2\text{Ph}$; and

m and n are integers independently chosen from 0-6.

13. A compound of claim 11 having the formula

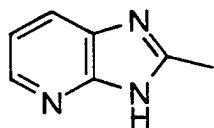
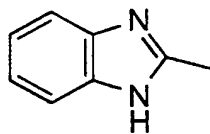
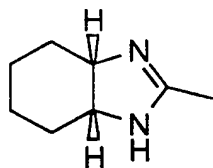
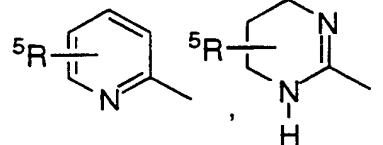
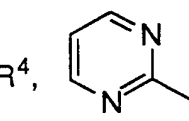
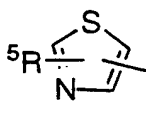
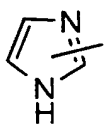
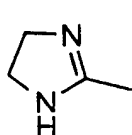
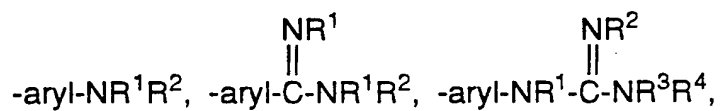
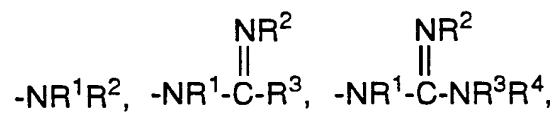


15

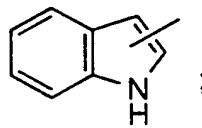
wherein

X is selected from the group consisting of

- 228 -



and



Y is selected from the group consisting of

C₁₋₈ alkylene,

(CH₂)_m-C≡C(CH₂)_n,

5 (CH₂)_mCR¹=CR²(CH₂)_n,

(CH₂)_mCR¹=CR²(CH₂)_nO,

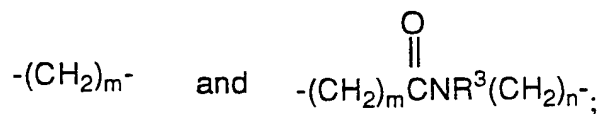
C₀₋₈ alkylene-NR³-CO-C₀₋₈ alkylene,

C₀₋₈ alkylene-O-C₀₋₈ alkylene,

C₀₋₈ alkylene-NR³-C₀₋₈ alkylene and

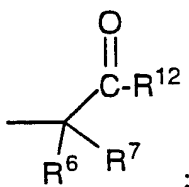
10 C₀₋₈ alkylene-NR³-C₀₋₈ alkylene-O-;

A is selected from the group consisting of



- 229 -

B is



R¹, R², R³ and R⁴ are each independently selected from the group consisting of

- 5 hydrogen,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 10 amino C₀₋₈ alkyl and
 aryl C₀₋₈ alkyl;

R⁵ is selected from the group consisting of

- hydrogen,
 15 C₁₋₄ alkoxy C₀₋₆ alkyl,
 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 amino C₀₋₈ alkyl,
 20 oxo and
 aryl C₀₋₈ alkyl;

R⁶ and R⁷ are each independently selected from the group consisting of:

- hydrogen,
 25 C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkyloxycarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl and
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl;

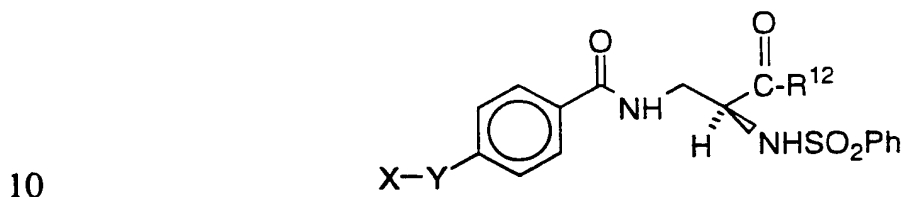
30

- 230 -

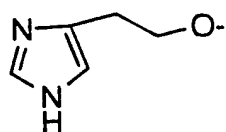
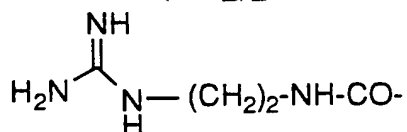
R¹² is selected from the group consisting of
 hydroxy,
 C₁₋₈ alkyloxy,
 C₁₋₆ dialkylaminocarbonylmethoxy and
 5 aryl C₀₋₆ dialkylaminocarbonylmethoxy, and

m and n are integers independently chosen from 0-6;

provided that when the compound is

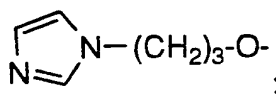


wherein R¹² is hydroxy or C₁₋₄ alkyloxy, then X-Y is not
 NH₂-(CH₂)₂-NH-CO-,
 BOC-HN-(CH₂)₂-NH-CO-,



15

or

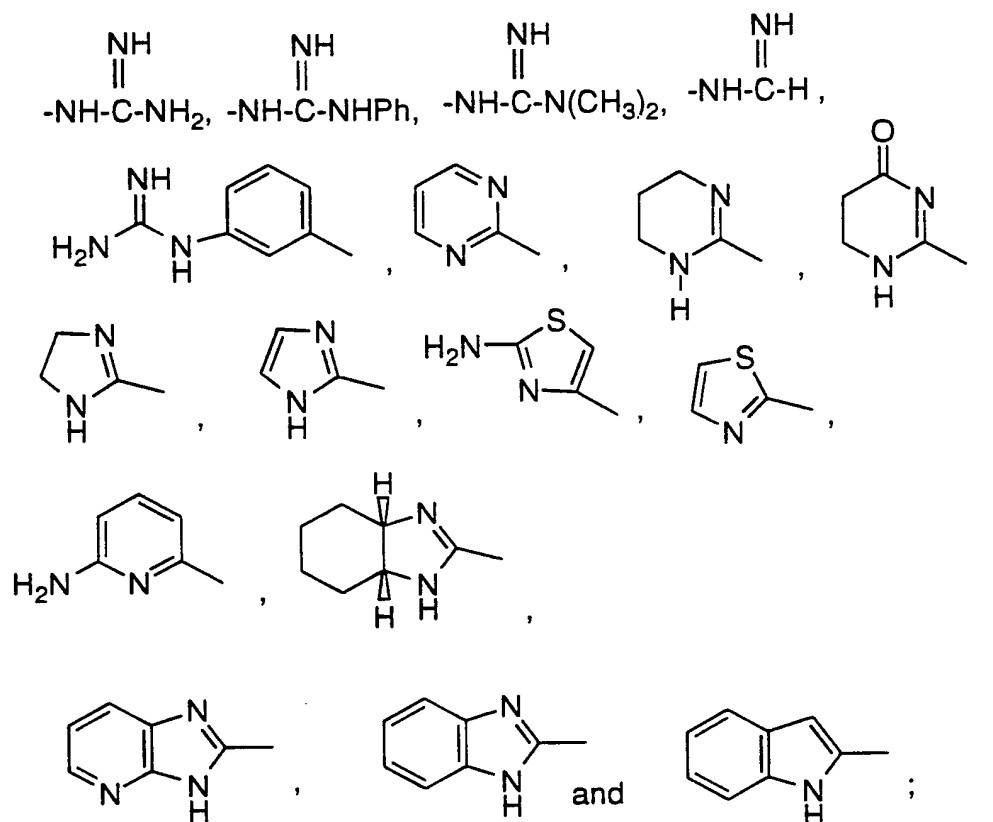


and the pharmaceutically acceptable salts thereof.

20

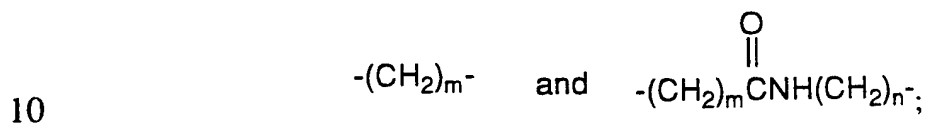
14. The compound of Claim 13, wherein
 X is selected from the group consisting of

- 231 -



Y is selected from the group consisting of
 C1-2 alkylene,
 C \equiv C-,
 5 C0-2 alkylene-NH-CO-,
 C0-5 alkylene-O-C0-1 alkylene and
 -NH-C2-4 alkylene-O-;

A is selected from the group consisting of



R¹ is selected from the group consisting of
 hydrogen and
 C1-4 alkoxy;

- 232 -

R⁶ and R⁷ are each independently selected from the group consisting of
hydrogen,
-NHCbz,
-NHSO₂Ph,
5 -NHC(O)-Ph, and
-N(CH₃)-SO₂Ph; and

m and n are integers independently chosen from 0-1.

10 15. The compound of Claim 14 selected from the group
of:

4-(2-Guanidoethyloxy)benzoyl-2(S)-benzyloxycarbonylamino-β-alanine,

15 4-(2-Guanidoethyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine,

2(S)-Phenylsulfonylamino-3-[4-(4-guanidobutyloxy)phenyl]-propionic
acid,

20 2(S)-(N-Benzyloxycarbonylamino)-3-[4-(5-guanidopentyloxy)phenyl]-
propionic acid,

4-(3-Guanidinoisopropoxy)benzoyl-2-(S)-phenylsulfonylamino-β-
alanine,

25 4-(3-Formamidinopropoxy)benzoyl-2-(S)-phenylsulfonylamino-β-
alanine,

30 3-Methoxy-4-(3-guanidinopropoxy)benzoyl-2(S)-phenylsulfonyl-
amino-β-alanine,

3-Methoxy-4-(3-aminopropoxy)benzoyl-2(S)-phenylsulfonylamino-β-
alanine,

- 233 -

- 3-[3-(Guanidino)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 5 4-[2-(N-Phenylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(N,N-Dimethylguanidino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 10 4-(Guanidinophen-3-yloxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(Guanidino)ethyloxymethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 15 3-[2-(Guanidino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester,
- 20 4-[2-(2-Aminothiazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 25 4-[2-(N-(2-Imidazolin-2-yl)aminoethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,
- 2(S)-Phenylsulfonylamino-3-[4-(4-(N-imidazolin-2-yl)aminobutyloxy)-phenyl]propionic acid,
- 30 4-[2-[N-[Cis-3a,4,5,6,7,7a-Hexahydro-1H-benzimidazol-2-yl]amino]-ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,

- 234 -

- 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-
β-alanine,
- 5 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-
phenylsulfonylamino-β-alanine,
- 4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-
alanine t-butyl ester,
- 10 4-[2-(2-Aminothiazol-4-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-
alanine,
- 4-[2(S)-(N-(2-Imidazolin-2-yl)amino)propyloxy]benzoyl-2(S)-phenyl-
sulfonylamino-β-alanine,
- 15 4-[2-(Imidazol-2-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine,
- 4-[2-(Thiazol-2-ylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-
alanine,
- 20 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-benzyloxycarbonyl-
amino-β-alanine,
- 4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-
25 benzyloxycarbonylamino-β-alanine,
- Methyl 2(S)-benzoylamino-3-[4-(4-pyrimidin-2-ylaminobutyloxy)-
phenyl]propionate,
- 30 2(S)-Benzoylamino-3-[4-(4-pyrimidin-2-ylamino)butyloxy]phenyl]-
propionic acid,
- 2(S)-Benzoylamino-3-[4-(4-(3,4,5,6-tetrahydropyrimidin-2-ylamino)-
butyloxy)phenyl]propionic acid,

- 235 -

4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-sulfonylamino- β -alanine t-butyl ester,

5 4-[2-(Pyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenyl-sulfonylamino- β -alanine,

4-[2-(3,4,5,6-Tetrahydropyrimidin-2-ylamino)ethyloxy]benzoyl-2(S)-N-methyl-N-phenylsulfonylamino- β -alanine,

10

4-[2-(N-(5,6-Dihydro-4-keto-1(H)-pyrimidin-2-yl)amino)ethyloxy]-benzoyl-2(S)-phenylsulfonylamino- β -alanine,

15 4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonyl-amino- β -alanine t-butyl ester,

4-(2-Aminopyridin-6-ylethynyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine,

20 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine,

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine t-butyl ester,

25

4-[2-(2-Aminopyridin-6-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,

30 4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine methyl ester,

4-[2-(Indol-2-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine,

- 236 -

4-[2-(1H-Imidazo[4,5-6]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine t-butyl ester,

5 4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethenyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine,

4-[2-(1H-Imidazo[4,5-b]pyridin-2-yl)ethyl]benzoyl-2(S)-phenyl-sulfonylamino- β -alanine,

10 4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)phenylsulfonylamino- β -alanine t-butylester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)phenylsulfonylamino- β -alanine t-butyl ester,

15 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7yl)ethyl]benzoyl-2(S)phenylsulfonylamino- β -alanine,

20 4-[2-(1,8-Naphthyridin-7-yl)ethenyl]benzoyl-2(S)phenylsulfonylamino- β -alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)phenylsulfonylamino- β -alanine ethyl ester,

25 4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylamido] β -alanine ethyl ester,

4-[2-(1,2,3,4-Tetrahydro-1,8 naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylamido] β -alanine,

30 4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido- β -alanine ethyl ester,

- 237 -

4-[(3-Aminoisoquinolin-1-yl)ethynyl]benzoyl-2(S)-phenylsulfonamido-
β-alanine trifluoroacetate,

4-[2-(3-Aminoisoquinolin-1-yl)ethyl]benzoyl-2(S)-phenylsulfonamido-
5 β-alanine trifluoroacetate,

4-[3-[N-(1H-Benzimidazo-2-yl)amino]propoxy]benzoyl-2(S)-
phenylsulfonylamino-β-alanine t-butyl ester, and

10 4-[3-[N-(1H-Benzimidazol-2-yl)amino]propoxy]benzoyl-2(S)-
phenylsulfonylamino-β-alanine.

16. A method of inhibiting the bone resorption activity
of mammalian osteoclast cells comprising the step of administering a
15 pharmacologically effective amount of a compound of Claim 13.

17. A composition for inhibiting bone resorption activity
of mammalian osteoclast cells comprising a pharmacologically effective
amount of the compound of Claim 13 and a pharmaceutically acceptable
20 carrier.

18. A method of inhibiting the bone resorption activity
of mammalian osteoclast cells comprising the step of administering a
pharmacologically effective amount of a compound of Claim 15.
25

19. A composition for inhibiting bone resorption activity
of mammalian osteoclast cells comprising a pharmacologically effective
amount of a compound of Claim 15 and a pharmaceutically acceptable
carrier.
30

20. A method for inhibiting tumor metastasis in a patient
comprising the step of administering a pharmacologically effective
amount of a compound of Claim 13.

- 238 -

21. A composition for inhibiting tumor metastasis in a patient comprising a pharmacologically effective amount of a compound of Claim 13 and a pharmaceutically acceptable carrier.

5 22. A method for inhibiting restenosis in a patient comprising the step of administering a pharmacologically effective amount of a compound of Claim 13.

10 23. A composition for inhibiting restenosis in a patient comprising a pharmacologically effective amount of a compound of Claim 13 and a pharmaceutically acceptable carrier.

15 24. A method for inhibiting diabetic retinopathy in a patient comprising the step of administering a pharmacologically effective amount of a compound of Claim 13.

20 25. A composition for inhibiting diabetic retinopathy in a patient comprising a pharmacologically effective amount of a compound of Claim 13 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/05938

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.
US CL : Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A,478,328 [EGBERTSON ET AL] 01 APRIL 1992, page 7, Formula III, lines 22-46	1-25
X	EP, A. 478,363 [LASWEL ET AL] 01 APRIL 1992, the whole document, and Formula I on page 2	1-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* "A"	document defining the general state of the art which is not considered to be of particular relevance	* "T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* "E"	earlier document published on or after the international filing date	* "X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* "L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* "Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* "O"	document referring to an oral disclosure, use, exhibition or other means	* "&"	document member of the same patent family
* "P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

10 AUGUST 1995

Date of mailing of the international search report

29 AUG 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Y.N. GUPTA

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/05938

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

A61K 31/18, 31/19, 31/44, 31/47, 31/195, 31/405, 31/415, 31/425, 31/435; CO7C 63/00, 307/06, 307/08, 307/10;
CO7D 213/89, 217/08, 233/44, 233/88, 239/08, 239/42, 209/40

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

514/275, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/332; 546/118, 122, 143, 290, 291,
301, 304, 309, 310, 311, 312; 548/195, 300.1, 308.4, 335.5, 495; 560/34; 564/86, 147

B. FIELDS SEARCHED Minimum documentation searched Classification System: U.S.

514/275, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/332; 546/118, 122, 143, 290, 291,
301, 304, 309, 310, 311, 312; 548/195, 300.1, 308.4, 335.5, 495; 560/34; 564/86, 147